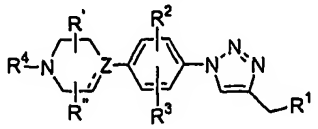
Novel triazole compounds as antibacterial agents and their pharmaceutical compositions containing them

Field of the Invention

The present invention relates to novel triazole compounds of formula (I),



(I)

where all symbols are as defined in the detailed description;

their pharmaceutically acceptable salts their stereosiomers thereof, their prodrugs, their rotamers, their pharmaceutical compositions containing them.

The present invention also relates to a process for the preparation of the above said novel compounds.

Background of the Invention

Since the discovery of penicillin, pharmaceutical companies have produced more than one hundred antibacterial agents to combat a wide variety of bacterial infections. In the past several years, there has been rapid emergence of bacterial resistance to several of these antibiotics. The multidrug resistance among these bacterial pathogens may also be due to mutation leading to more virulent clinical isolation; the most disturbing milestone has been the acquisition of resistance to vancomycin, an antibiotic generally regarded as the agent of last resort for serious Gram-positive infections. This growing multidrug resistance has recently rekindled interest in the search for new structural class of antibiotic that inhibit or kill these bacteria possibly by novel mechanisms.

A problem of larger dimension is the increasing incidence of the more virulent, methicillin-resistant *Staphylococcus aureas* (MRSA) among clinical isolates found worldwide. As with vancomycin resistant organisms, many MRSA strains are resistant to most of the known antibiotics, but MRSA strains have remained sensitive to vancomycin. However, in view of the increasing reports of vancomycin resistant clinical isolates and growing problem of bacterial resistance, there is an urgent need for new molecular entities effective against the emerging and currently problematic Gram-positive organisms.

Recently, several oxazolidinones have been discovered, which inhibit protein synthesis by binding to the 50S-ribosomal subunit which is close to the site to which chloramphenicol and lincomycin bind but their mode of action is mechanistically distinct from these two antibiotics.

Various 1, 2, 3-triazoles, 1, 2, 4-triazoles and benzotriazoles have been reported to show various biological activities and have therefore found applications in medicinal chemistry.

Some of the literature references are:

(a) Chem. Pharm. Bull. 48(12), 1935-1946 (2000) discloses the triazoles of reported as antifungal agents,

(b) US 6054471 discloses fluorinated triazoles, which are reported for the treatment of neuropathic pain and associated hyperalgesia, including trigeminal and herpectic neuralgia, diabetic neuropathic pain, migraine, causalgia and deafferentation syndromes such as brachial plexus avulsion,

(c) J. Med. Chem., 2843, 1991 discloses compound, which is an anticoccidiostat and also been found to have antiproliferative activity in several disease models and to posses antimetastatic activity in a model of ovarian cancer progression,

(d) J. Heterocycl. Chem., 609, 1989 discloses compound, which is reported for anti-inflammatory effects,

(e) EPO publication no 0304221 A2 discloses compounds, which are reported as antiproliferative reagents.

(f) PCT publication no. WO03/059894 (by Dr. Reddy's Laboratories Ltd.) discloses 1,2,3-triazoles as antibacterial agents.

The novel triazole compound of the present invention is useful for the treatment of various infections

Summary of the Invention

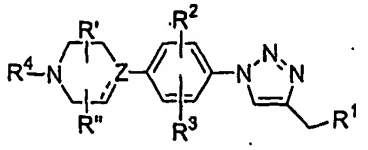
According to one aspect of the present invention, there is provided novel triazole compounds of the general formula (I) as defined above, their pharmaceutically acceptable salts their stereosiomers thereof, their prodrugs, their rotamers, their pharmaceutical compositions containing them.

Another aspect of the present invention provides a process for the preparation of novel triazole compounds of the formula (I).

Yet another aspect of the pesent invention provides the use of novel compounds of formula (I) or their pharmaceutical compositions in the treatment of bacterial infections.

Detailed description of the Invention

The present invention relates to compounds having the general formula (I),



(I)

Where R^1 is isoindole-1,3-dione, azido, NHR^5 where R^5 represents

(a) Hydrogen,

(b) $-\overset{\overset{Q}{\|}}{C}-R^6$

Where Q represents 'O' or 'S'

R^6 represents

(i) Hydrogen,

Optionally substituted groups selected from,

(ii) Alkyl,

(iii) Cycloalkyl,

(iv) Alkoxy,

(v) Cycloalkoxy,

(vi) Alkenyl,

(vii) Alkenyloxy,

(viii) Aryl,

(ix) Aryloxy,

(x) Heteroaryl,

(xi) Heterocyclyl,

(xii) Heteroaryloxy,

(xiii) -NH-R^7, where R^7 represents hydrogen, optionally substituted groups selected from alkyl, cycloalkyl, hydroxyalkyl, alkoxy, cycloalkoxy, alkenyl, aryl, aralkyl, heteroaryl, heteroaralkyl,

$-\overset{\overset{Q}{\|}}{C}-R^8$ ' wherein R^8 is optionally substituted group selected from alkyl, alkoxy, cycloalkyl, alkenyl, alkenyloxy, aryl, aryloxy, aralkyl, aralkoxy, heteroaryl, heteroaryloxy, and Q represents oxygen or sulfur;

(xiv) -N-[alkyl]$_2$,

(xv) -N(R^cR^d), wherein R^c and R^d together form an optionally substituted 5 or 6 member heterocycle ring containing nitrogen and optionally having one or two additional hetero atoms selected from O, S or N;

(xvi) -SR^8, wherein R^8 is as defined above,

(xv) -SO_2-alkyl;

R^2 and R^3 at each occurrence are the same or different and are

(i) Hydrogen,

(ii) Halogen,

(iii) Cyano,

(iv) Nitro,

(v) Amino

Optionally substituted groups selected from

(vi) Alkyl,

(vii) Haloalkyl,

(viii) OR^a where R^a represents hydrogen or optionally substituted alkyl group;

(ix) -NR^b where R^b represents hydrogen or optionally substituted alkyl, alkenyl, cycloalkyl, alkoxy, hydroxyalkyl, alkyl carbonyl, alkoxycarbonyl, alkoxyalkyl, carboxyalkyl, alkylsulfonyl, alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, alkylcarbonyloxyalkyl, amino alkyl, alkylamino, aryl amino;

'Z' represents N, C or CH;

'.....' represents a bond or nobond;

R^4 represents hydrogen, cyano, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylamino, alkylaminoalklyl, acyl, haloacyl, alkylcarbonyl, alkoxycarbonyl,, hydroxyalkylcarbonyl, alkoxyalkyl, alkenyloxy, aryl, aryloxy, arylcarbonyl, aralkyl, aralkylcarbonyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, heteroaralkylcarbonyl, heterocyclylalkyl, heteroaryloxy, cycloalkoxy, heteroarylcarbonyl, heterocyclylcarbonyl, alkenylcarbonyl, aralkyl, aralkoxyalkyl, aralkoxyalkylcarbonyl, alkenylcarbonyl, aralkylcarbonyl, aralkoxyalkylcarbonyl, alkylsulfonyl, alkylsulfanyl, alkylsulfinyl, arylsulfonyl, arylsulfanyl, arylsulfinyl, *tert*-butoxycarbonyl, (BOC), heteroarylsulfonyl

R' and R'' independently represent hydrogen, oxo (=O), thioxo (=S), amino, cynao; halogen, alkyl, alkoxy or haloalkyl;

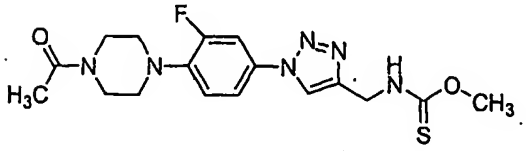
Substituents on R^4, R^6, R^7, R^8, independently selected from halogen, nitro, cyano, amino, hydroxy, cyano, oxo (=O), thioxo (=S), =N-CN, =N-OR^x, where R^x represents hydrogen, alkyl or aryl; optionally substituted groups selected from alkyl, cycloalkyl, alkoxy, alkenyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyl, alkylamino, aminoalkyl, alkylaminoalkyl, aminocarbonyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, alkylsulfinyl, alkylsulfanyl, acyl, aryl, aralkyl, aralkoxy, heteroaryl, *tert*-butyl-dimethyl-silanyloxy)-acetyl chloride (TBDMSO), *tert*-butoxycarbonyl (BOC), N-hydroxyformamide, carboxylic acids or its derivatives, phosphoric acid or its derivates. Further optional substituents on the optionally substituted groups defined above are selected from halogen, hydroxyl, cyano, amino, nitro, oxo (=O), thioxo (=S), hydroxyalkyl, alkylamino, aminoalkyl, carboxylic acid or its derivatives.

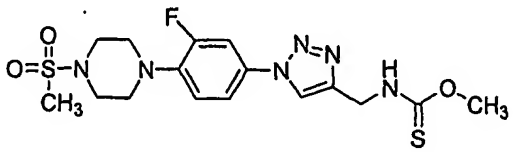
Substitutents on R^2 and R^3 independently selected from hydroxy, halogen, nitro, amino, alkyl, haloalkyl, alkoxy, =O, =S, cyano group, or carboxylic acid or its derivatives.

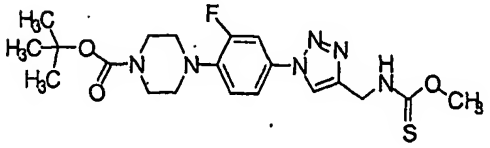
their pharmaceutically acceptable salts their stereosiomers thereof, their prodrugs, their rotamers, their pharmaceutical compositions containing them.

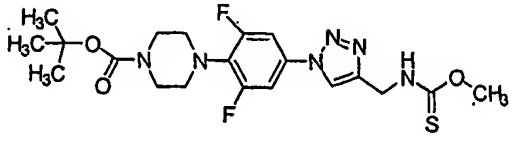
Wherever substitutions are possible on the groups represented by R^2, R^3, R^4, R^5, R^6, R^7 and R^8, they may take place 1 to 5 times, which may be same or different;

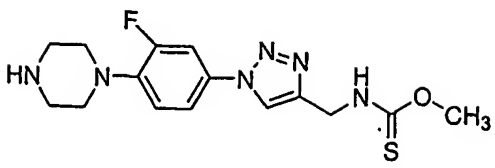
Representative compounds in accordance with the present invention are presented in Table 1. This table is not intended to be exclusive of the compounds of the present invention, but rather exemplary of the compounds that are encompassed by this invention

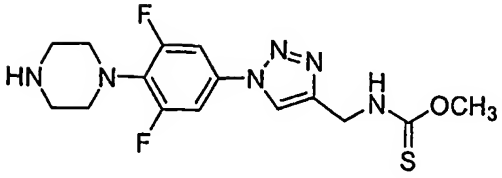


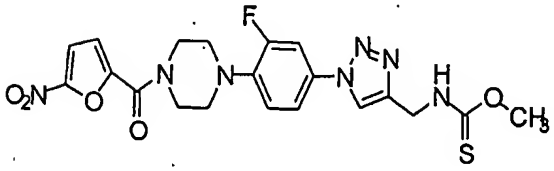


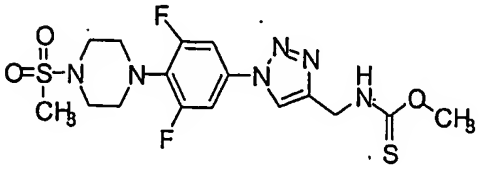


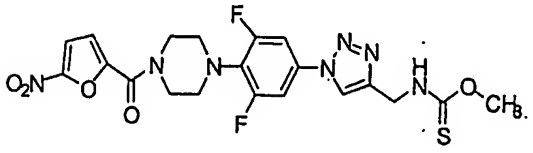


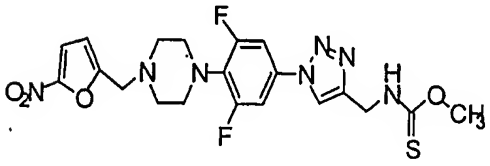


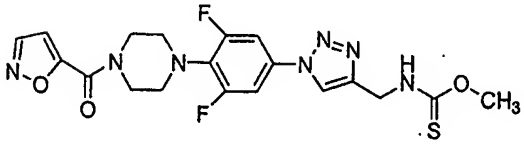


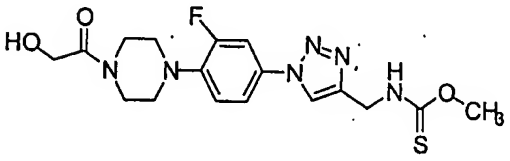


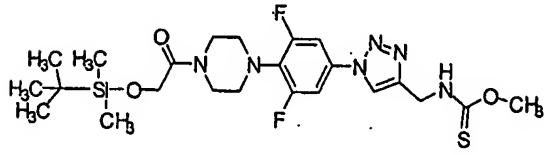


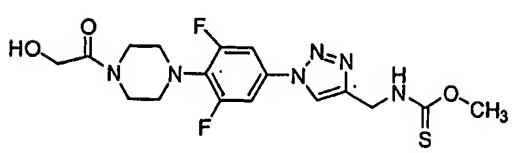


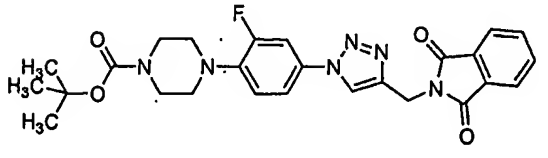


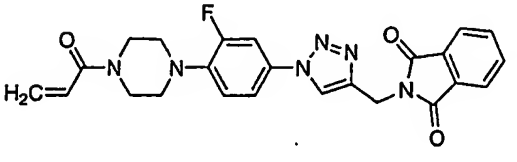


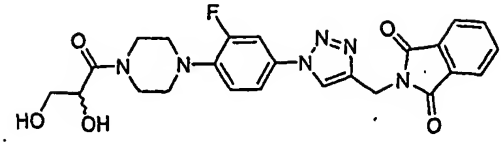


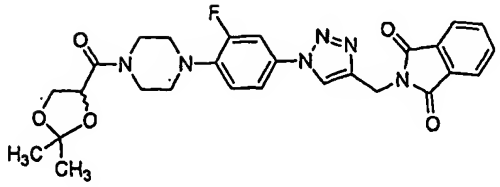


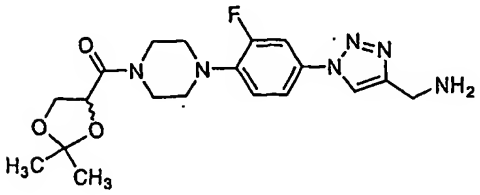


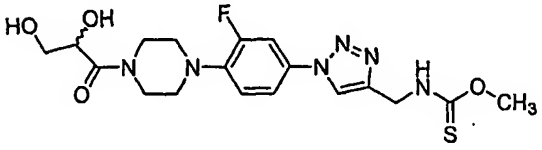


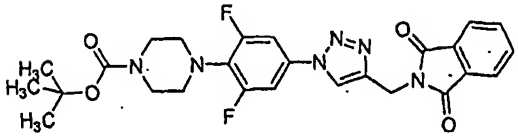


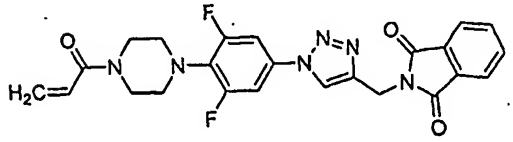


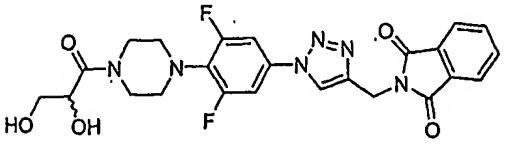


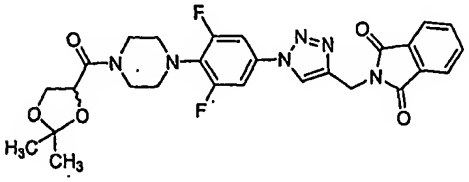


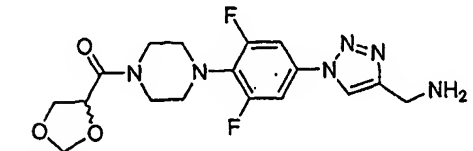


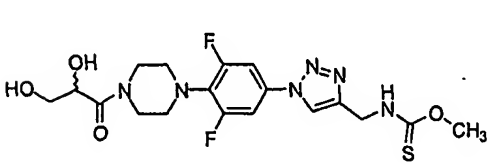


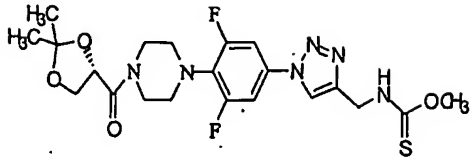


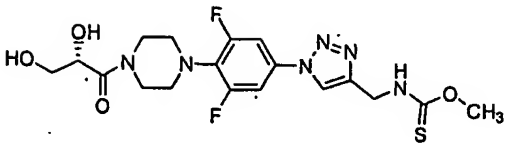


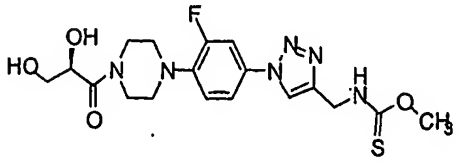


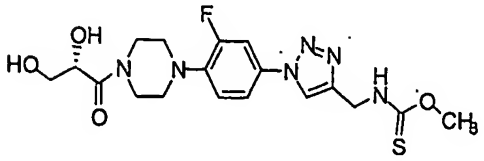


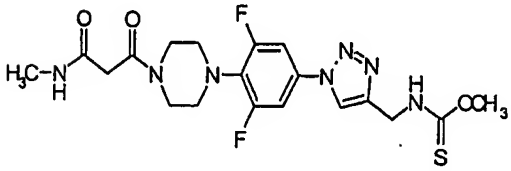


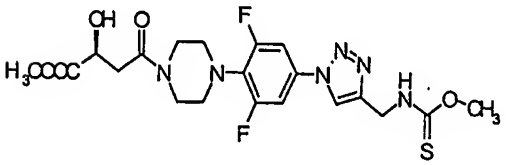


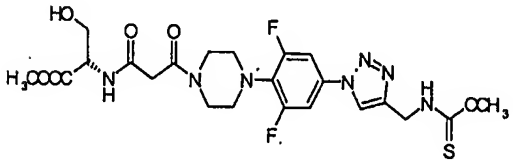


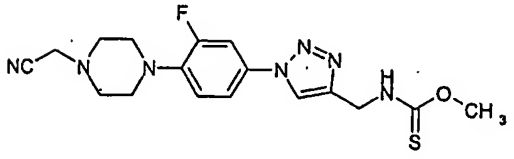


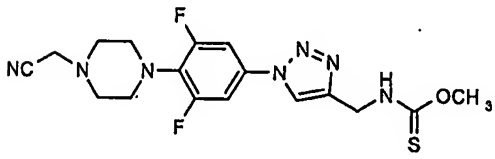


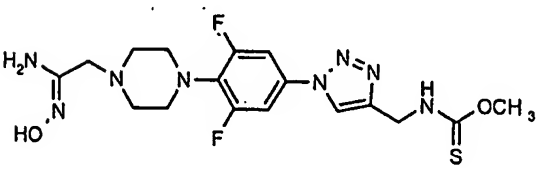


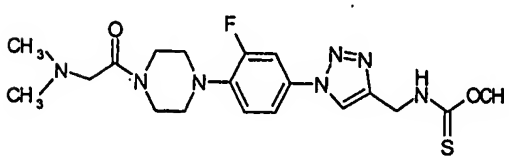


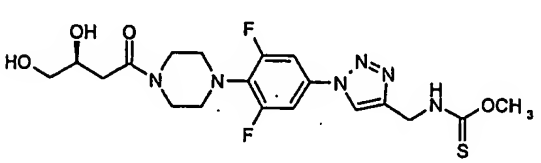


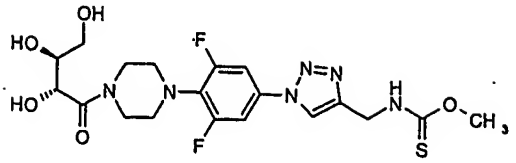


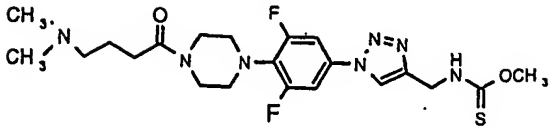


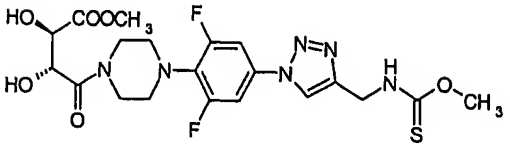


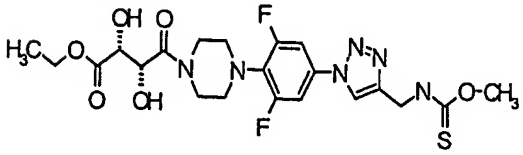


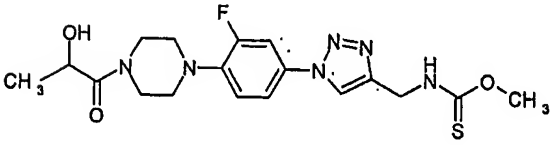


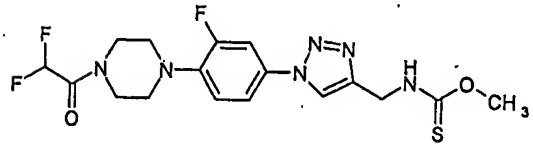


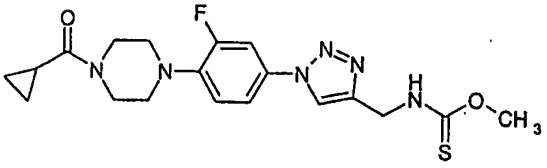


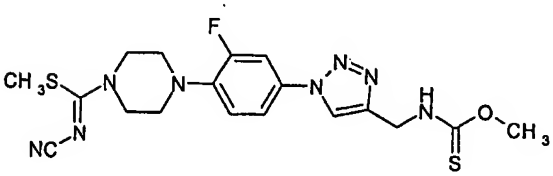


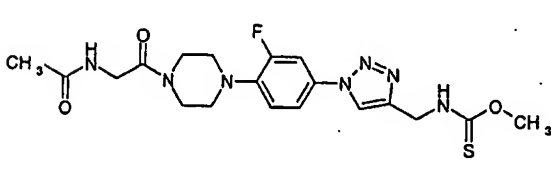


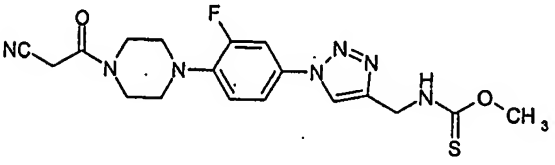


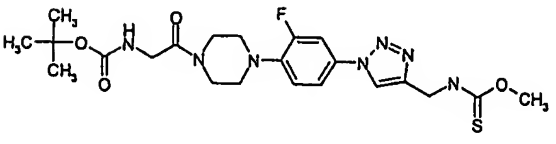


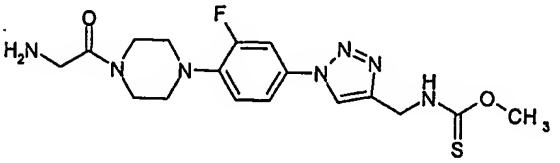


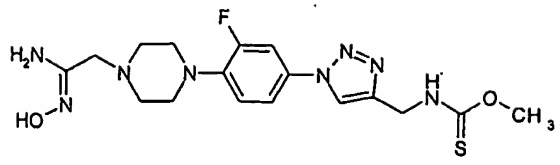


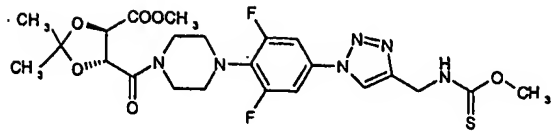


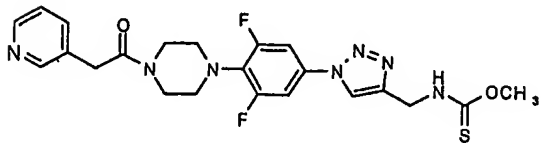


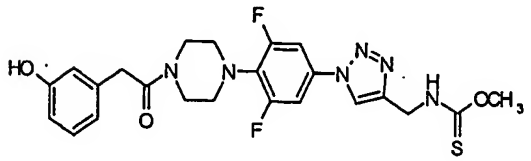


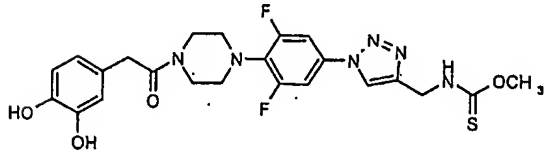


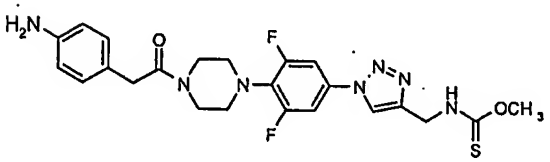


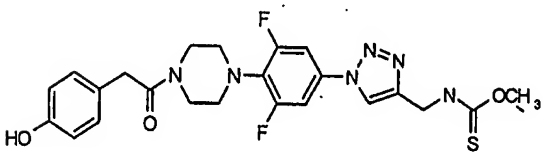


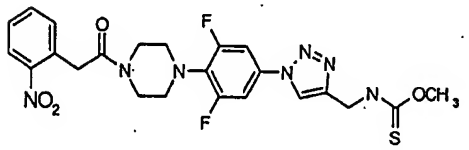


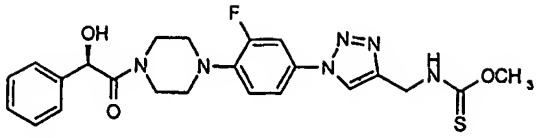


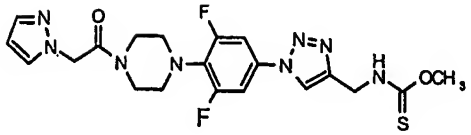


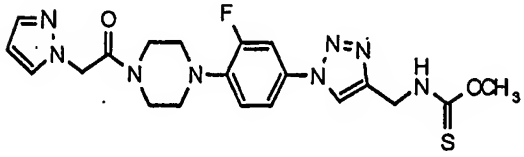


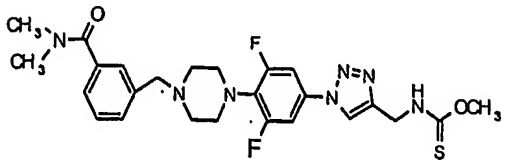


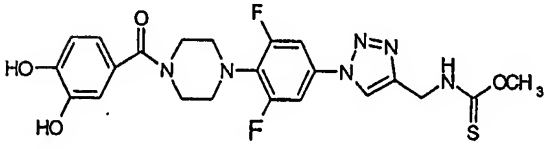


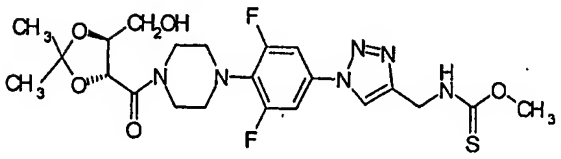


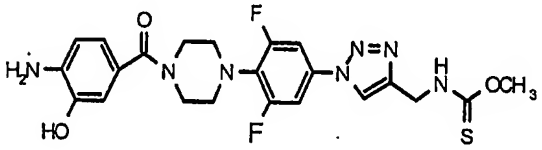


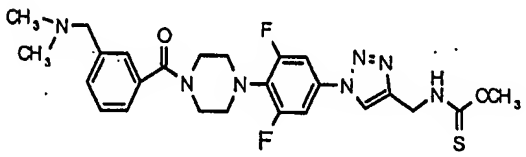


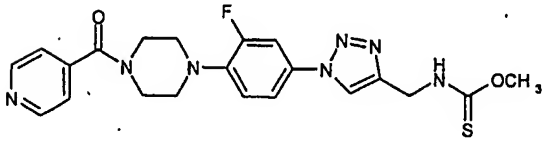


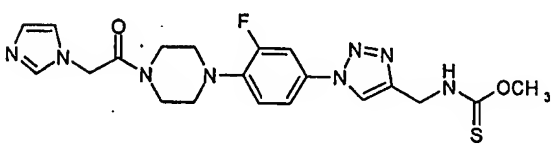


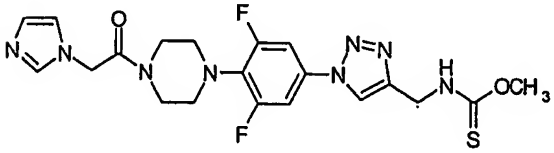


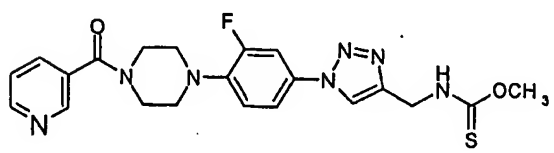


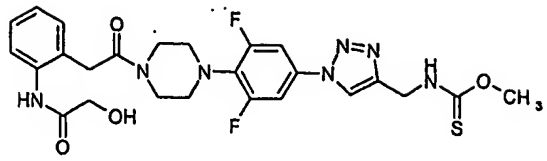


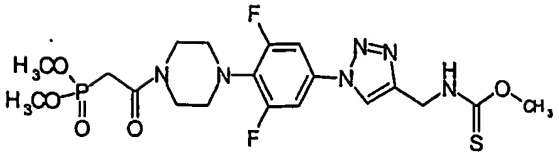


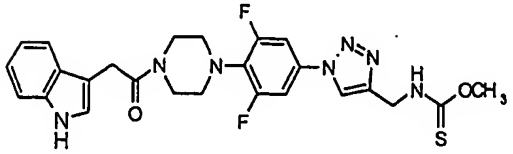


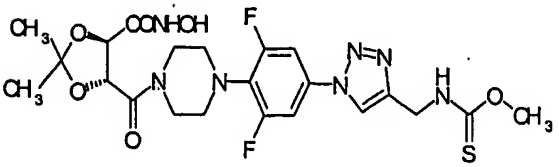


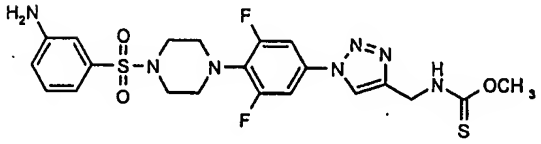


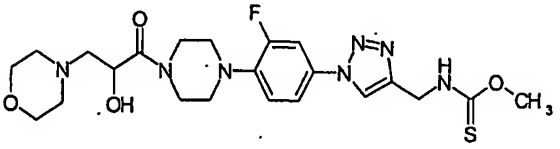


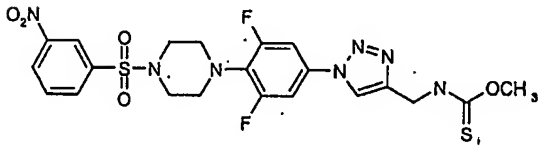


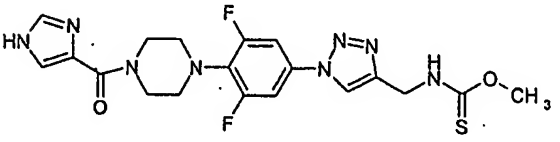


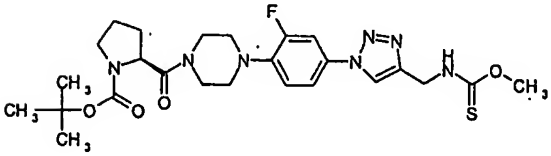


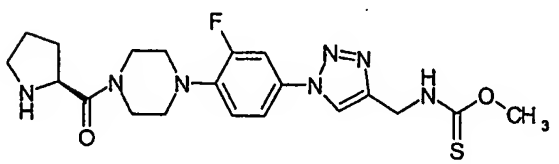


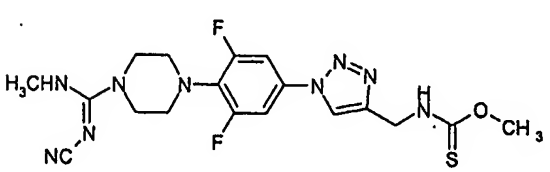


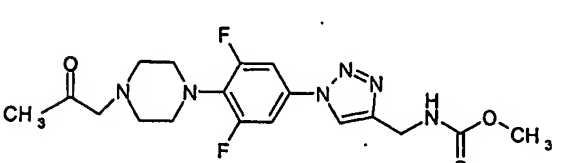


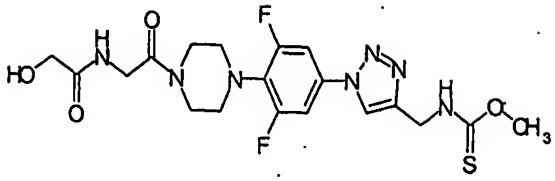


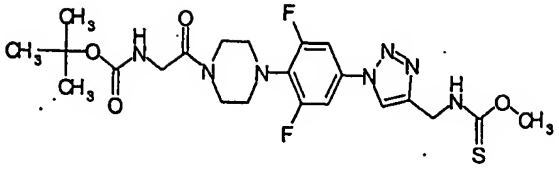


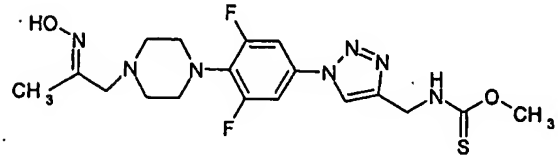


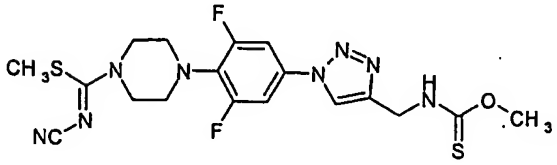


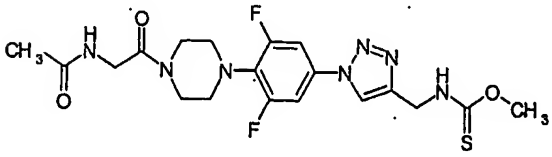


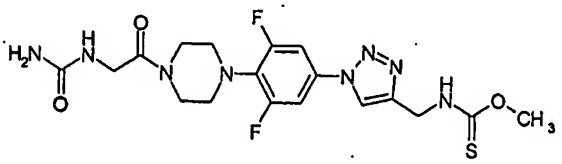


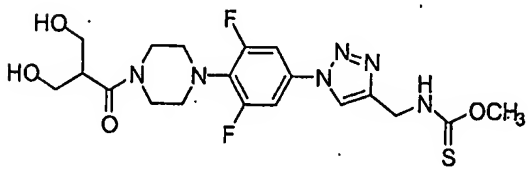


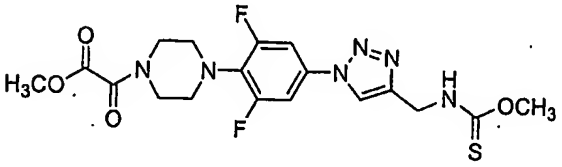


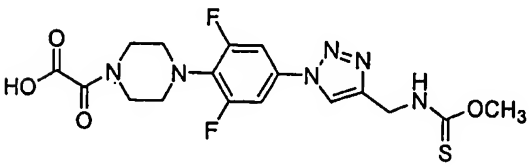


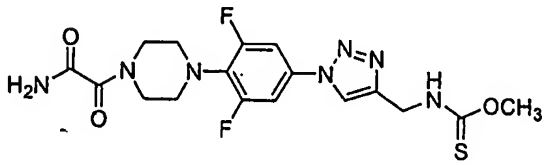


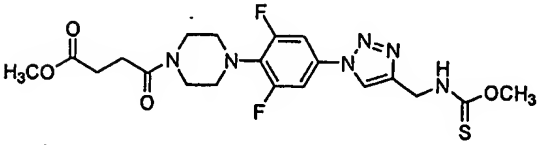


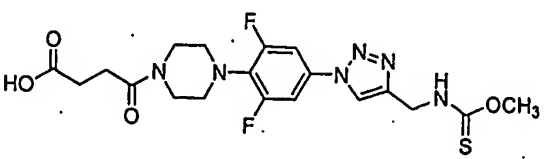


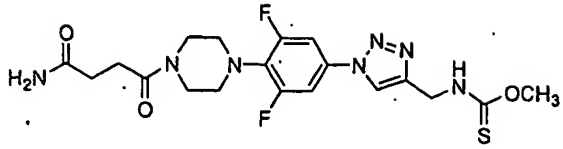


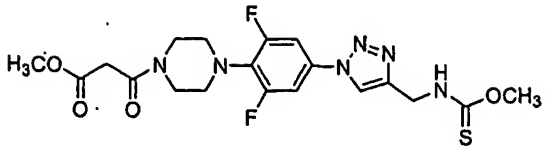


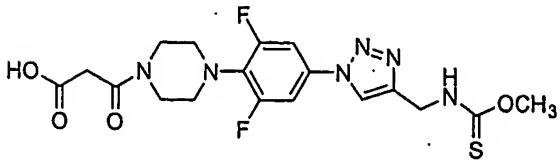


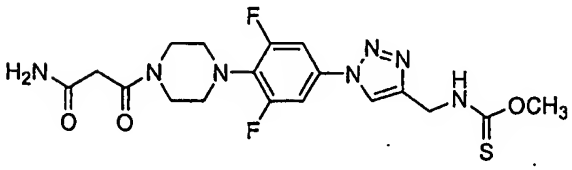


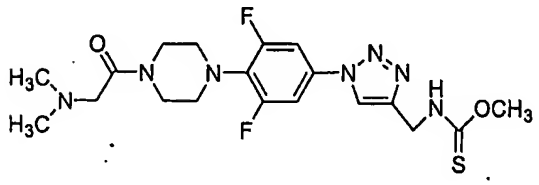


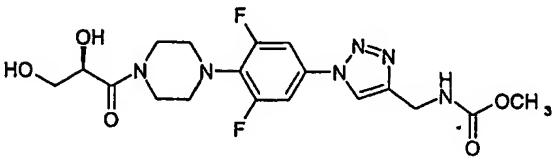


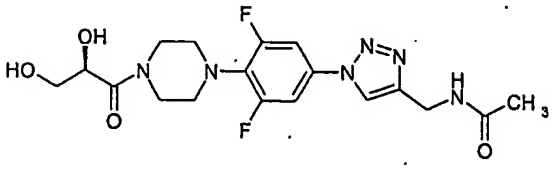


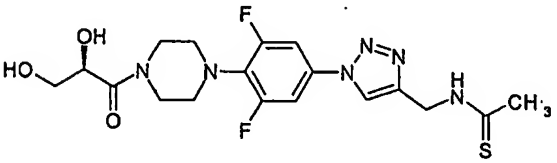


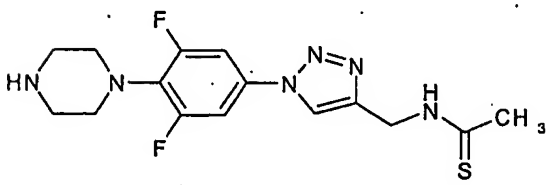


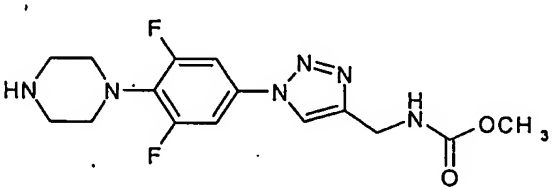


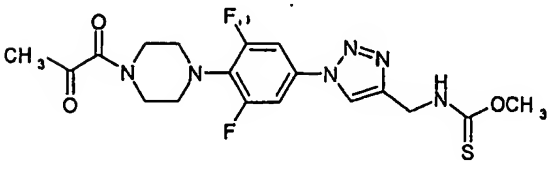


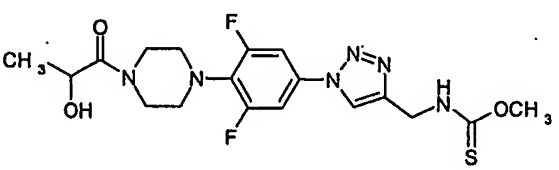


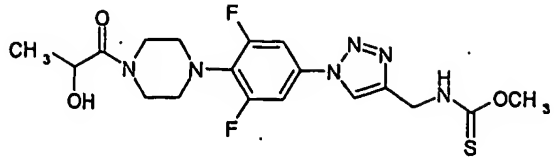


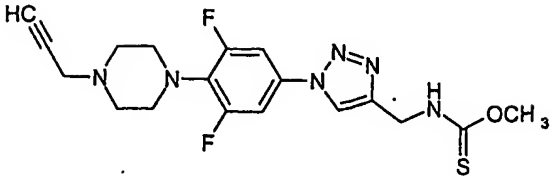


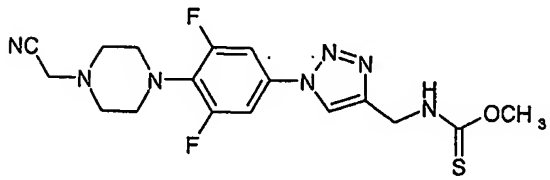


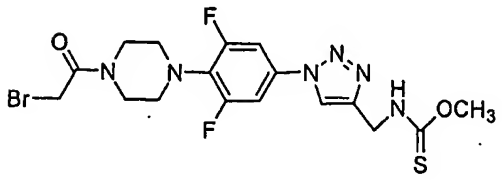


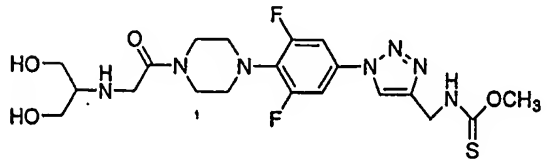


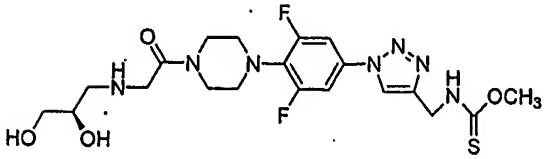


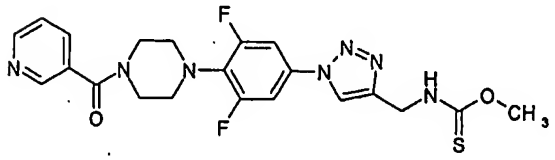


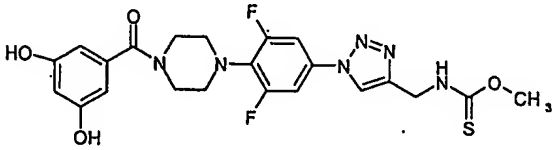


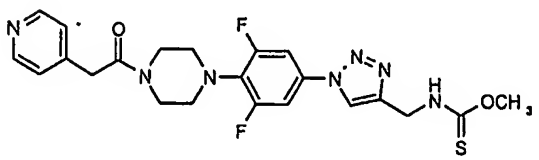


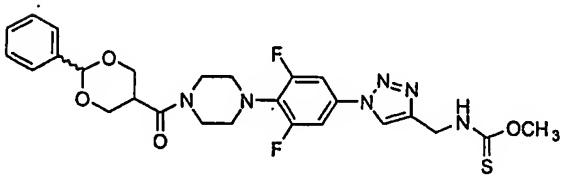


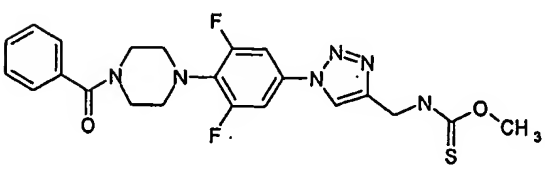


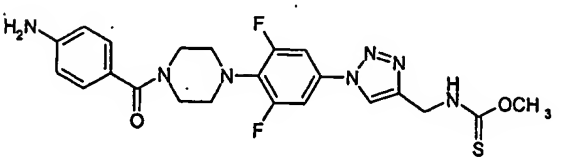


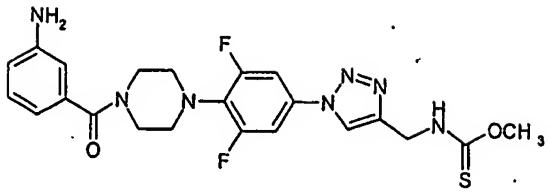


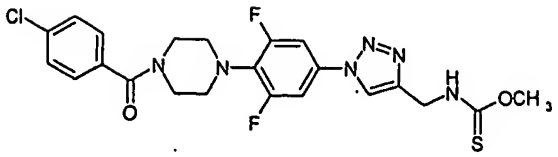


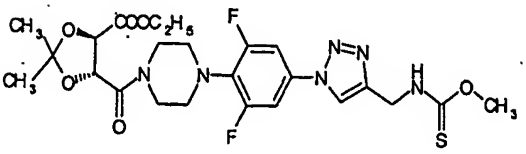


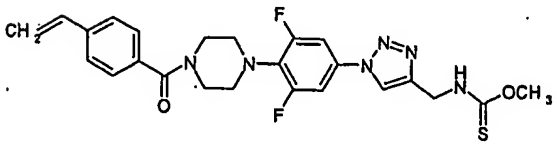


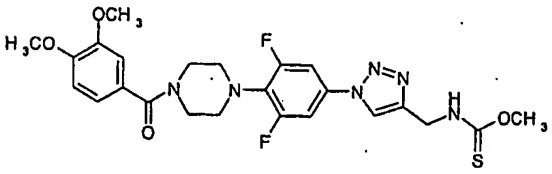


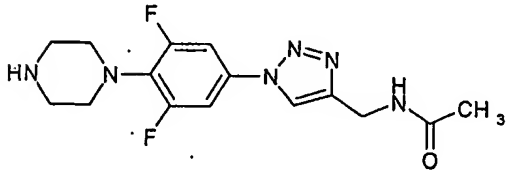


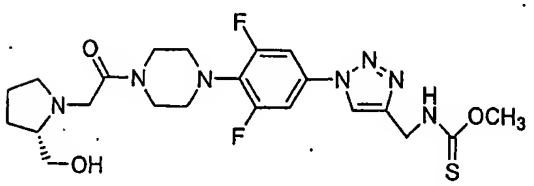


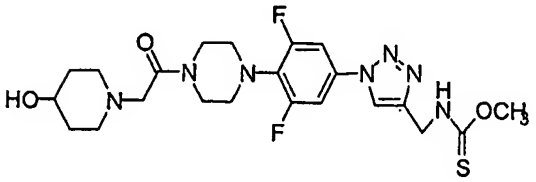


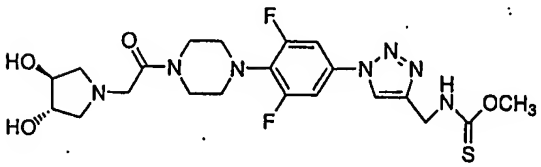


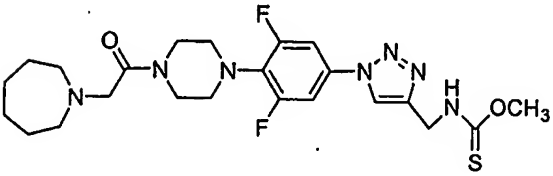


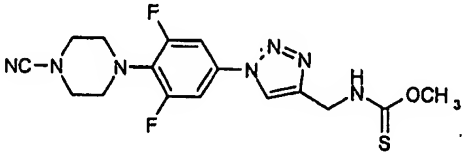


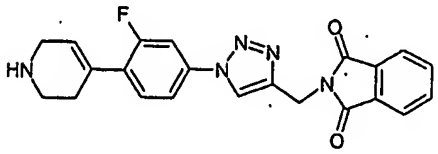


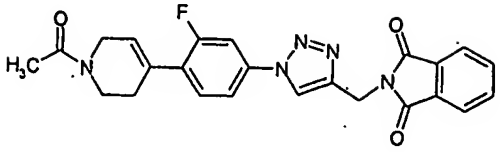


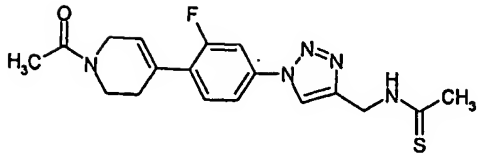


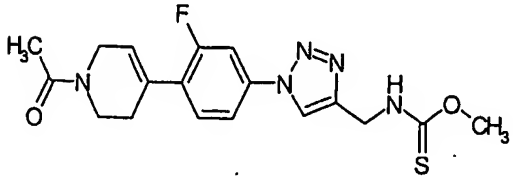


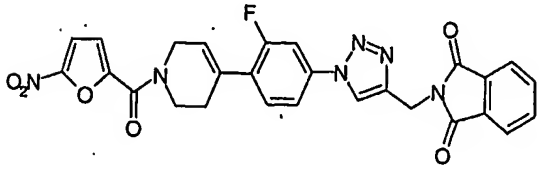


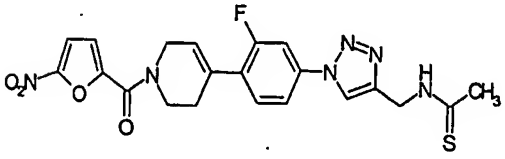


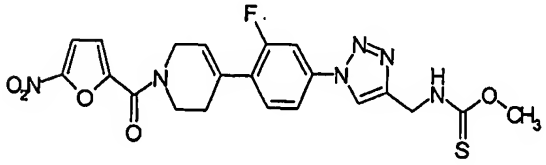


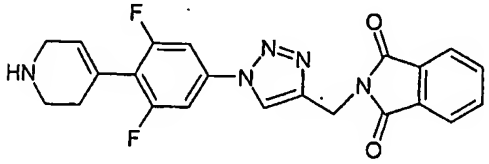


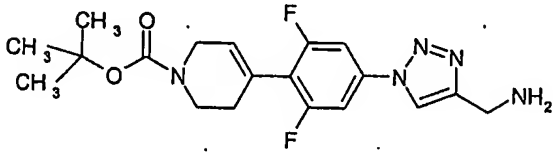


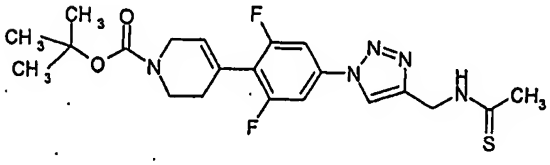


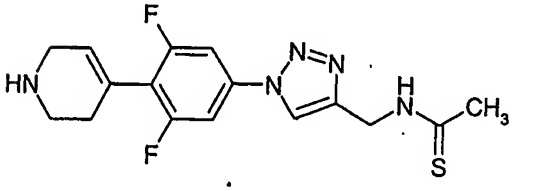


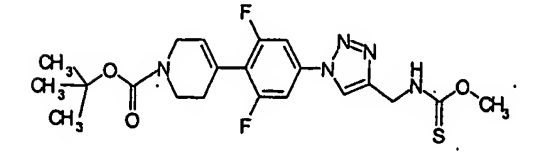


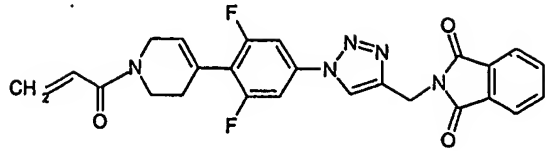


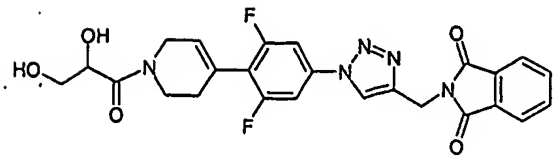


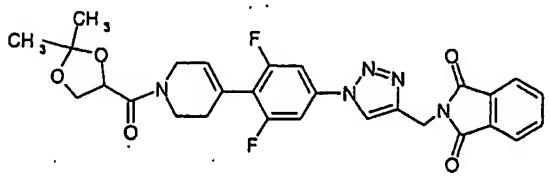


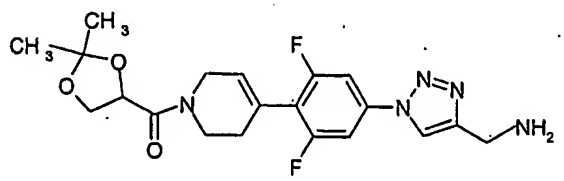


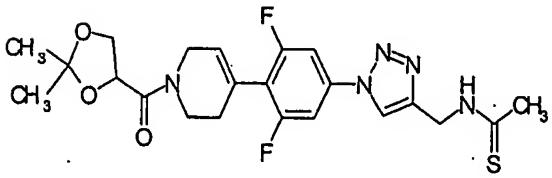


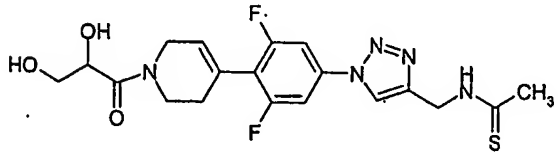


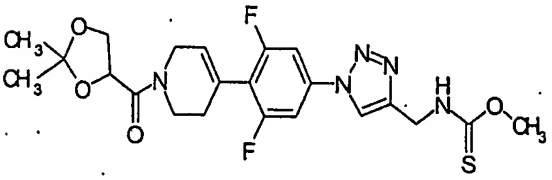


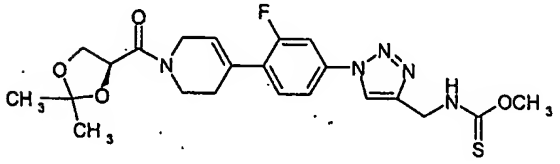


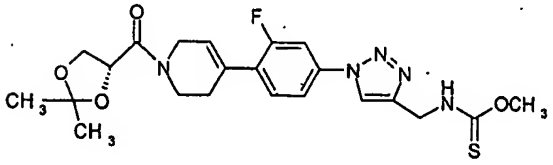


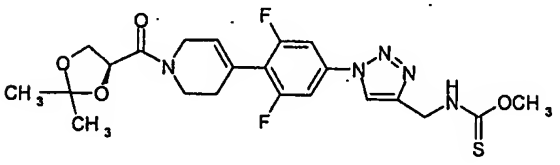


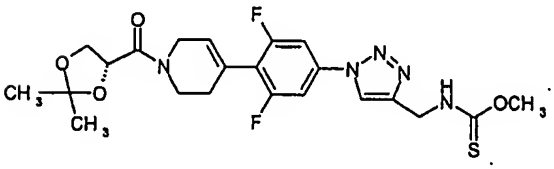


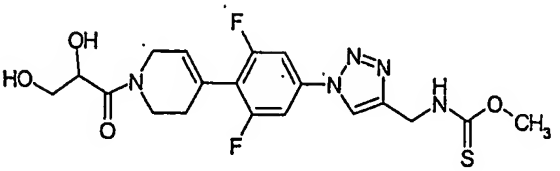


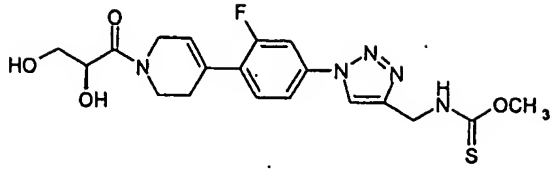


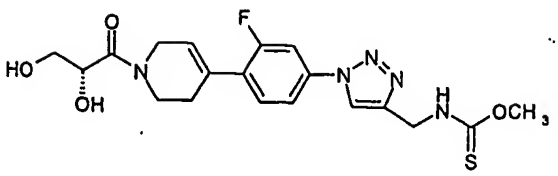


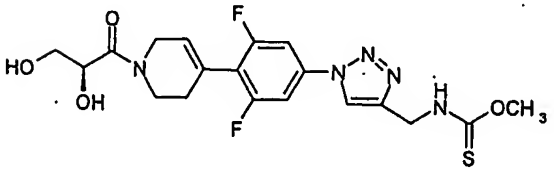


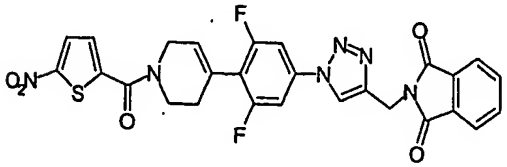


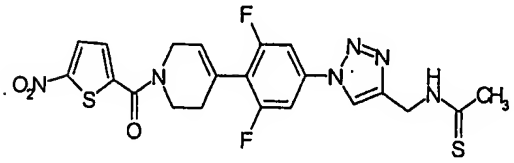


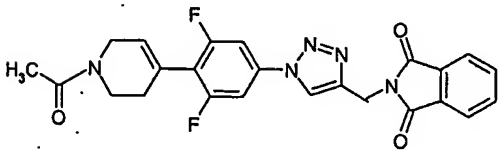


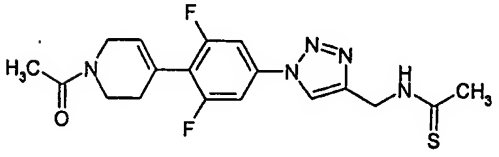


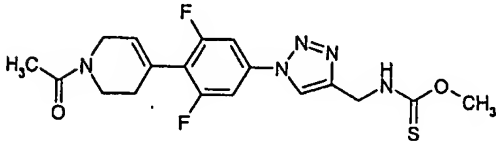


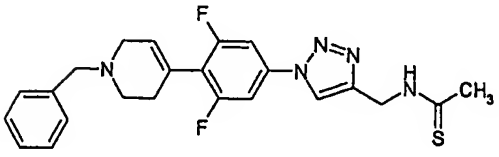


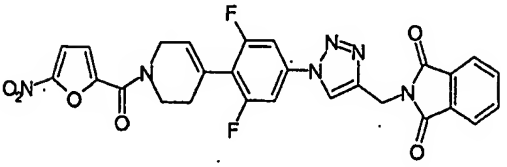


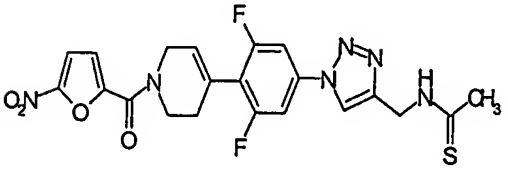


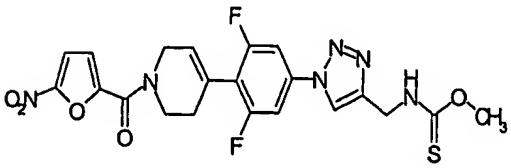


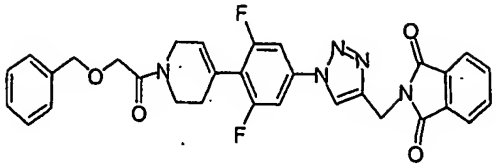
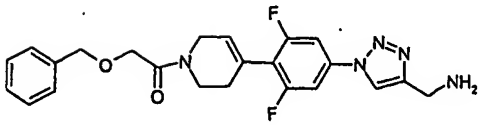
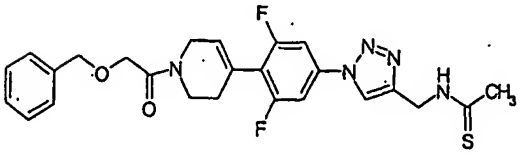
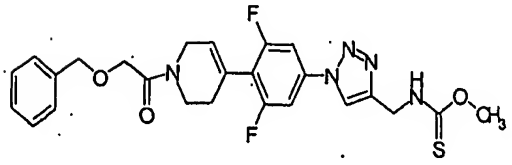
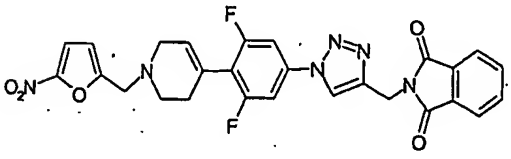
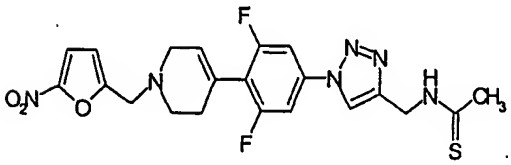
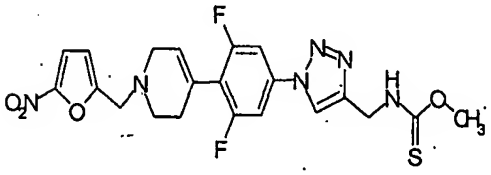
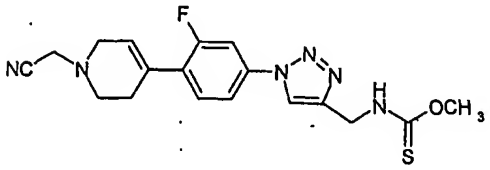
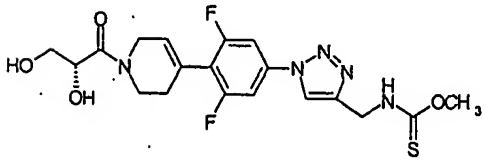
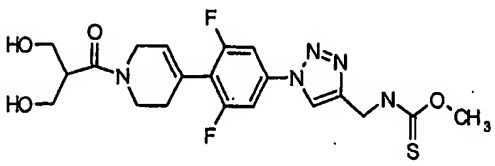
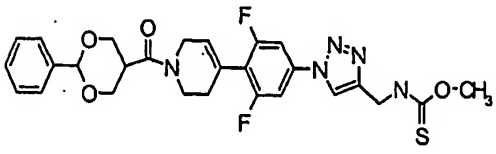






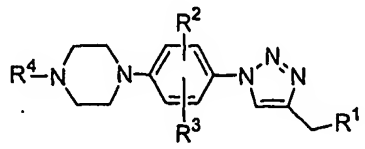




their stereoisomers and their pharmaceutically acceptable salts thereof;

One aspect of the present invention provides compound of formula (I), where Z represents 'N', '.....' represents no bond, which is represented by compound of formula (Ia); their pharmaceutically acceptable salts their stereosiomers thereof, their pharmaceutical compositions containing them


(Ia)

Where R^1 represents

Where Q represents 'S'

R^6 represents

(i) Hydrogen,

Optionally substituted groups selected from,

(ii) Alkyl,

(iii) Cycloalkyl,

(iv) Alkoxy,

(v) Cycloalkoxy,

(vi) Alkenyl,

(vii) Alkenyloxy,

R^2 and R^3 at each occurrence are the same or different and are

(i) Hydrogen,

(ii) Halogen,

R^4 represents hydrogen, cyano, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, hydroxyalkyl, haloalkyl, aminoalkyl, alkylamino, alkylaminoalklyl, acyl, haloacyl, aminocarbonyl, alkylcarbonyl, cycloalkylcarbonyl, alkoxycarbonyl,, hydroxyalkylcarbonyl, alkoxyalkyl, aryl, aryloxy, arylcarbonyl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, heteroaralkylcarbonyl, heteroaryloxy, cycloalkoxy, heteroarylcarbonyl, heterocyclylcarbonyl, heterocyclylalkylcaarbonyl, *tert*-butoxycarbonyl (BOC), alkenylcarbonyl, aralkyl, aralkylcarbonyl, aralkoxyalkylcarbonyl, alkenylcarbonyl, alkylsulfonyl, alkylsulfanyl, alkylsulfinyl, arylsulfonyl, arylsulfanyl, arylsulfinyl, heteroarylsulfonyl

Substituents on R^4 selected from halogen, nitro, cyano, amino, hydroxy, oxo (=O), =N-CN, =N-OR^x, where R^x represents hydrogen, alkyl or aryl; optionally substituted groups selected from alkyl, cycloalkyl, alkoxy, alkenyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyl, alkylamino, aminoalkyl, alkylaminoalkyl, aminocarbonyl; alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, alkylsulfinyl, alkylsulfanyl, acyl, aryl, aralkyl, aralkoxy, heteroaryl, (*tert*-butyl-dimethyl-silanyloxy)-acetyl chloride (TBDMSO), *tert*-butoxycarbonyl (BOC), N-hydroxyformamide, carboxylic acid or its derivatives. The optional substituents on these groups are selected from halogen, hydroxyl, cyano, amino, nitro, oxo (=O), hydroxyalkyl, alkylamino, aminoalkyl, carboxylic acid or its derivatives, phosphoric acid or its derivates;

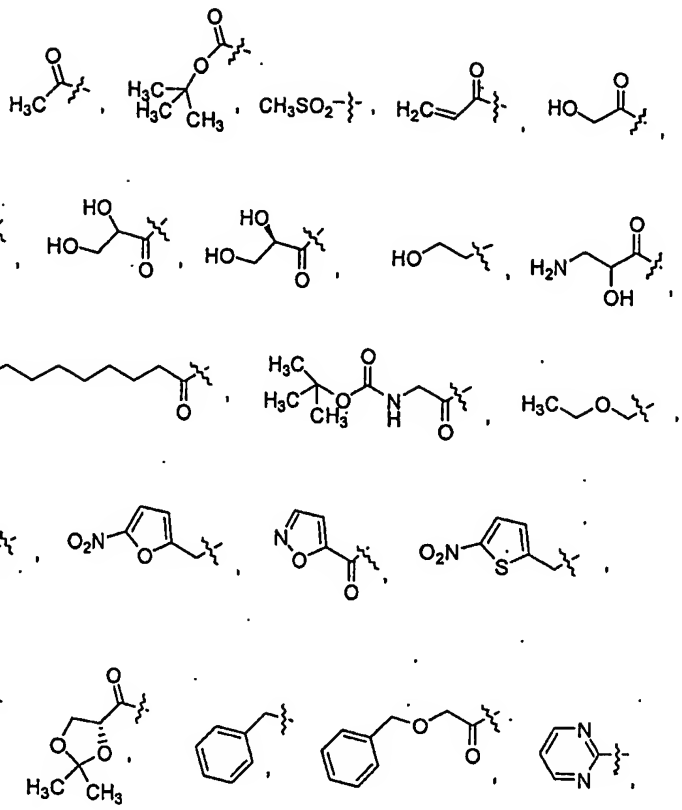
The substitutions on the possible groups represented by R^4, may take place 1 to 5 times, which may be same or different;

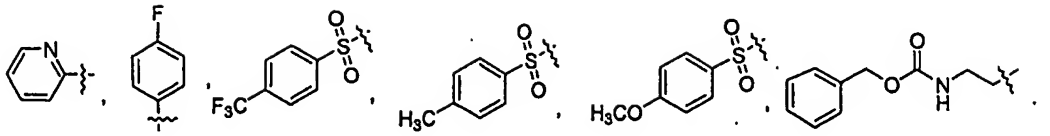
Another aspect of compound of formula (Ia), where R_1 represents

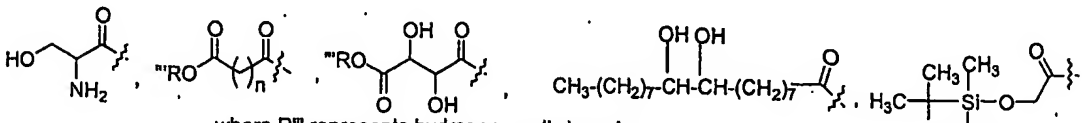
$-\overset{\overset{S}{\|}}{C}-R^6$, wherein R^6 represents alkyl or alkoxy group;

R^2 and R^3, which may be same or different, independently represent hydrogen or halogen;

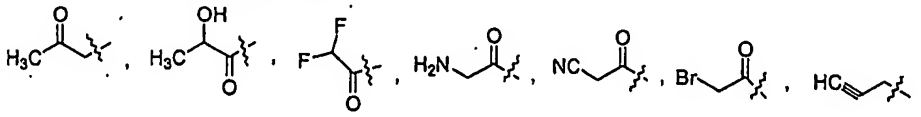
R^4 represents

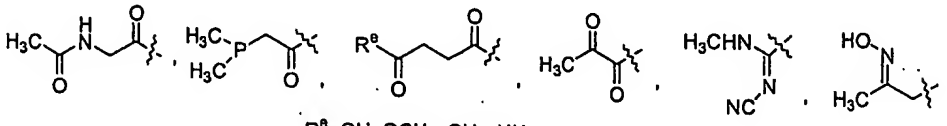
Hydrogen, Cyano 



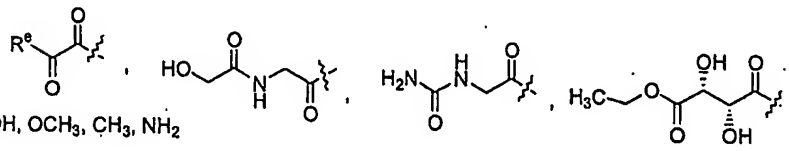


where R''' represents hydrogen or alkyl grou'p
n represents 0-6;

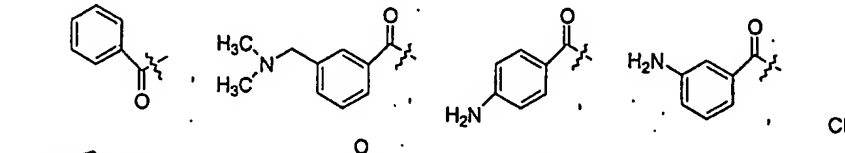


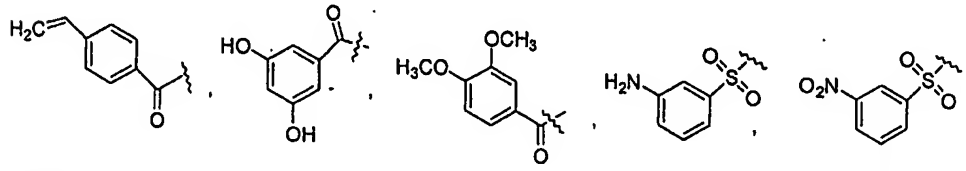


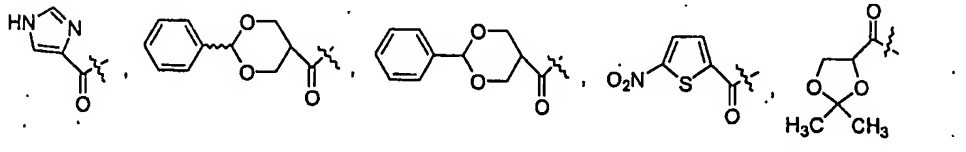
R^e=OH, OCH_3, CH_3, NH_2

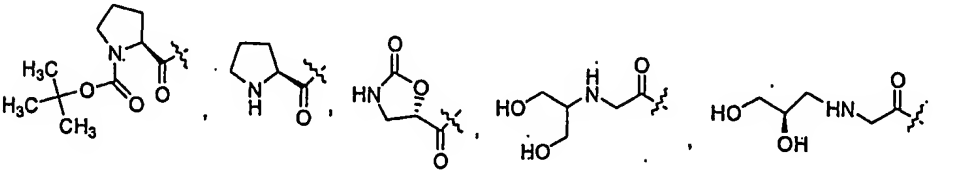


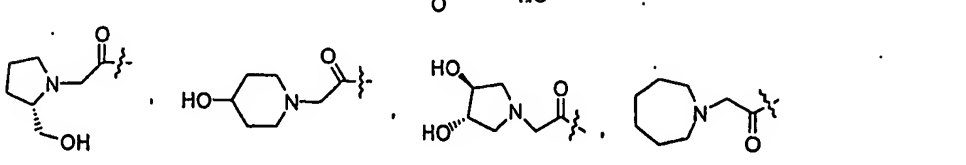
R^e=OH, OCH_3, CH_3, NH_2

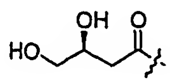


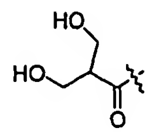


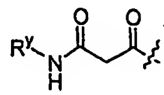




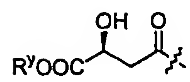




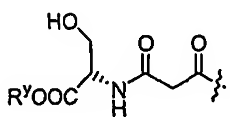




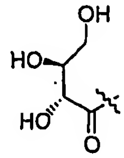
R^y represents alkyl or aryl

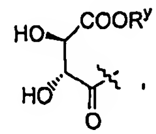


R^y represents alkyl or aryl

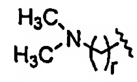


R^y represents alkyl or aryl

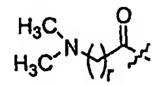




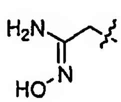
R^y represents alkyl or aryl

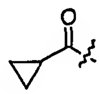


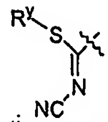
r =0-6



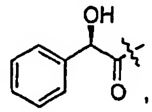
r =0-6

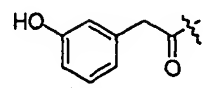


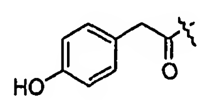


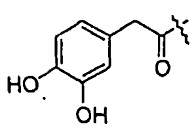


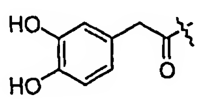
R^y represents alkyl or aryl

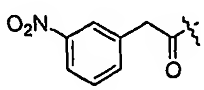


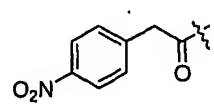


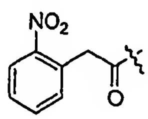


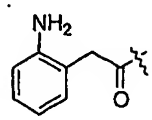


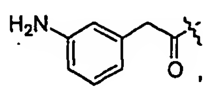


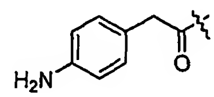


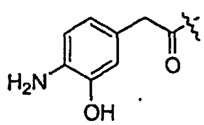


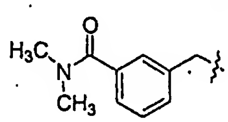


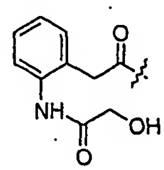


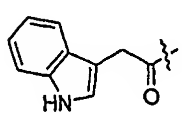


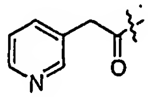


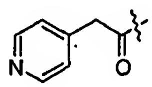


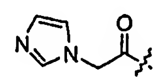


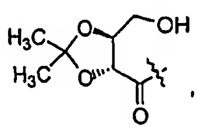


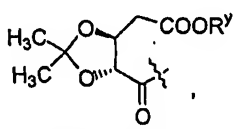




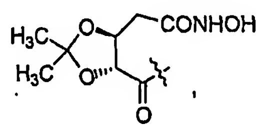


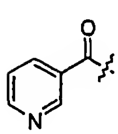


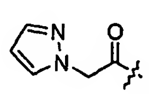


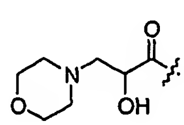


R^y represents alkyl or aryl







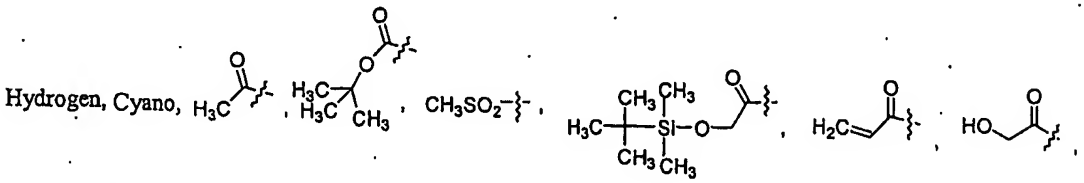


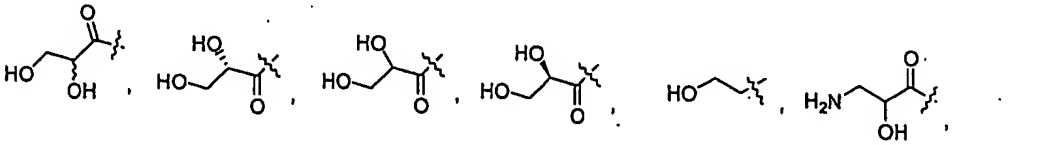
Another embodiment of compound of formula (Ia), where R_1 represents

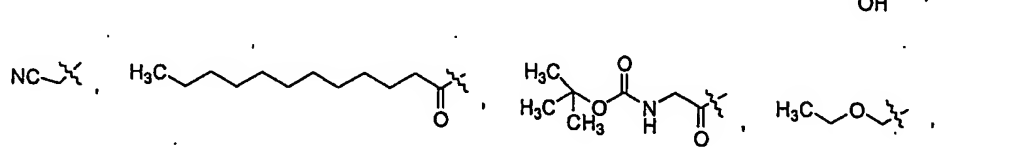
, wherein R^6 represents alkyl or alkoxy group;

R^2 and R^3, which may be same or different, independently represent hydrogen or halogen;

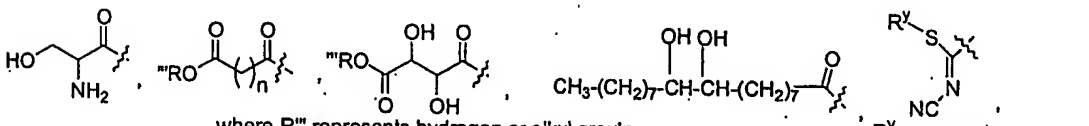
R^4 represents

Hydrogen, Cyano, 



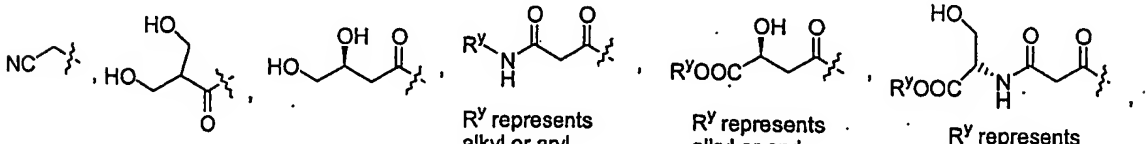


where R'''' represents hydrogen or alkyl grou'p
n represents 0-6;



where R'''' represents hydrogen or alkyl grou'p
n represents 0-6;

R^y represents alkyl or aryl



R^y represents alkyl or aryl

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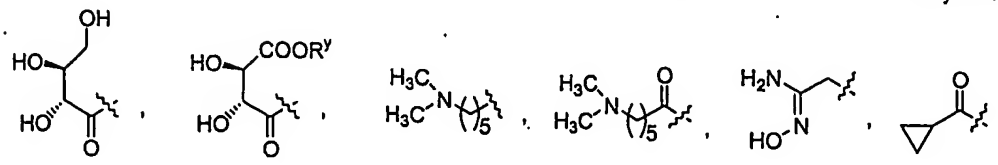


R^y represents alkyl or aryl

Another embodiment of compound of formula (Ia), where R_1 represents

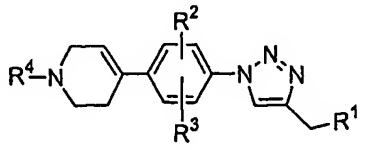
, wherein R^6 represents alkyl or alkoxy group;

R^2 and R^3, which may be same or different, independently represent hydrogen or halogen;

R^4 represents cyano,

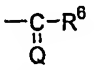
R^y represents alkyl or aryl

Another aspect of the present invention provides compound of formula (I), where 'Z' represents C, '.....' represents bond, which is represented by compound of formula (Ib); their pharmaceutically acceptable salts their stereosiomers thereof, pharmaceutical compositions containing them



(Ib)

Where R^1 represents



Where Q represents 'S'

R^6 represents

(i) Hydrogen,

Optionally substituted groups selected from,

(ii) Alkyl,

(iii) Cycloalkyl,

(iv) Alkoxy,

(v) Cycloalkoxy,

(vi) Alkenyl,

(vii) Alkenyloxy,

R^2 and R^3 at each occurrence are the same or different and are

(i) Hydrogen,

(ii) Halogen,

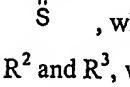
R^4 represents hydrogen, cyano, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, hydroxyalkyl, haloalkyl, aminoalkyl, alkylamino, alkylaminoalklyl, acyl, haloacyl, aminocarbonyl, alkylcarbonyl, cycloalkylcarbonyl, alkoxycarbonyl,, hydroxyalkylcarbonyl, alkoxyalkyl, aryl, aryloxy, arylcarbonyl, aralkyl, heterocyclyl, heterocyclylalkyl; heteroaryl, heteroaralkyl, heteroaralkylcarbonyl, heteroaryloxy, cycloalkoxy, heteroarylcarbonyl, heterocyclylcarbonyl, heterocyclylalkylcaarbonyl, *tert*-butoxycarbonyl (BOC), alkenylcarbonyl, aralkyl, aralkylcarbonyl, aralkoxyalkylcarbonyl, alkenylcarbonyl, alkylsulfonyl, alkylsulfanyl, alkylsulfinyl, arylsulfonyl, arylsulfanyl, arylsulfinyl, heteroarylsulfonyl

Substituents on R^4 selected from halogen, nitro, cyano, amino, hydroxy, oxo (=O), =N-CN, =N-OR^x, where R^x represents hydrogen, alkyl or aryl; optionally substituted groups selected from alkyl, cycloalkyl, alkoxy, alkenyl, haloalkyl, hydroxyalkyl, hydroxyalkylamino, hydroxyalkyl, alkylamino, aminoalkyl, alkylaminoalkyl, aminocarbonyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, alkylsulfinyl, alkylsulfanyl, acyl, aryl, aralkyl, aralkoxy, heteroaryl, (*tert*-butyl-dimethyl-silanyloxy)-acetyl chloride (TBDMSO), *tert*-butoxycarbonyl (BOC), N-hydroxyformamide, carboxylic acids or its derivatives. The optional substituents on these groups are selected from halogen, hydroxyl, cyano, amino, nitro, oxo (=O), hydroxyalkyl, alkylamino, aminoalkyl, carboxylic acid or its derivatives, phosphoric acid or its derivates;

The substitutions on the possible groups represented by R^4, may take place 1 to 5 times, which may be same or different;

which is represented by compound of formula (Ia); their pharmaceutically acceptable salts their stereosiomers thereof, pharmaceutical compositions containing them

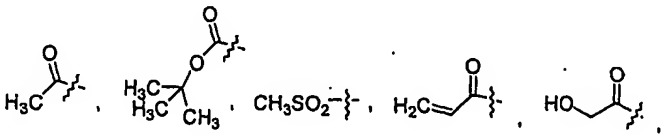
Another embodiment of compound of formula (Ib), where R_1 represents

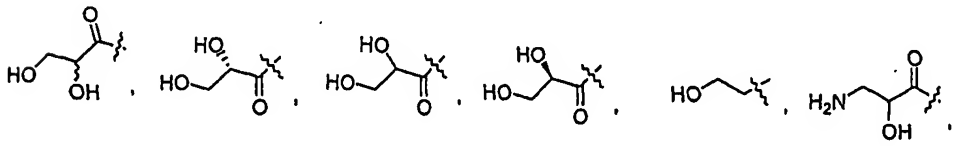


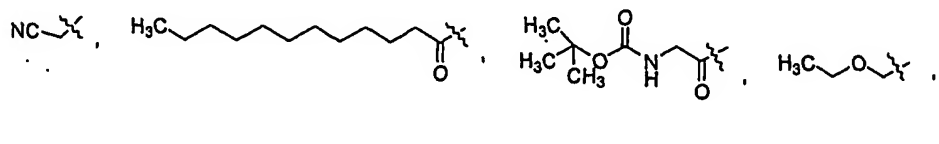
, wherein R^6 represents alkyl or alkoxy group;

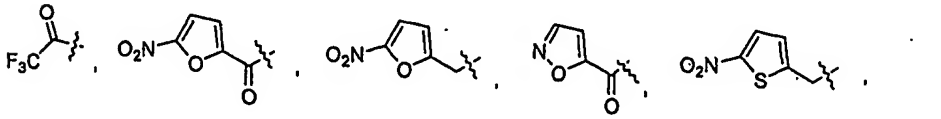
R^2 and R^3, which may be same or different, independently represent hydrogen or halogen;

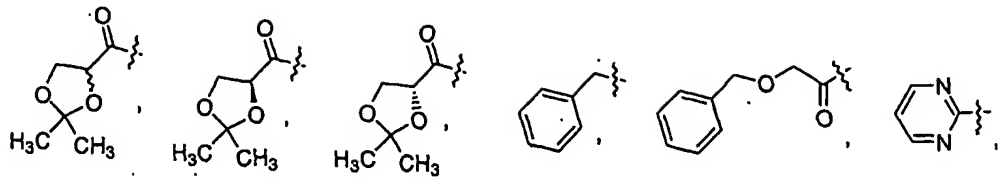
R^4 represents

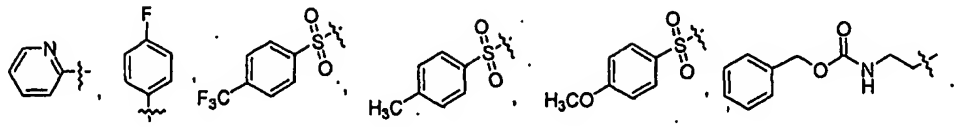
Hydrogen, Cyano, 

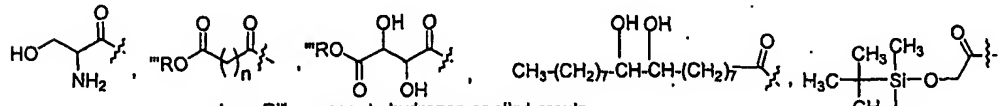




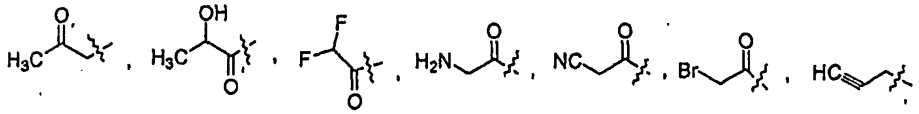


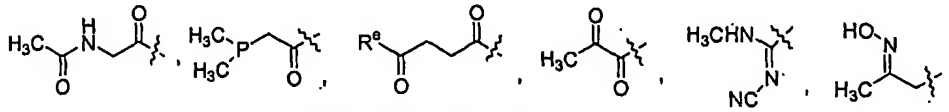




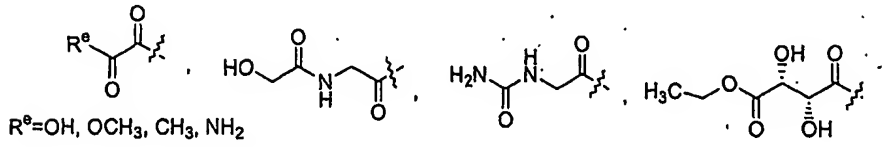


where R''' represents hydrogen or alkyl grou'p
n represents 0-6;

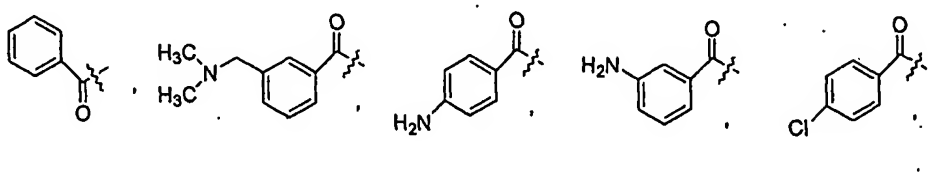


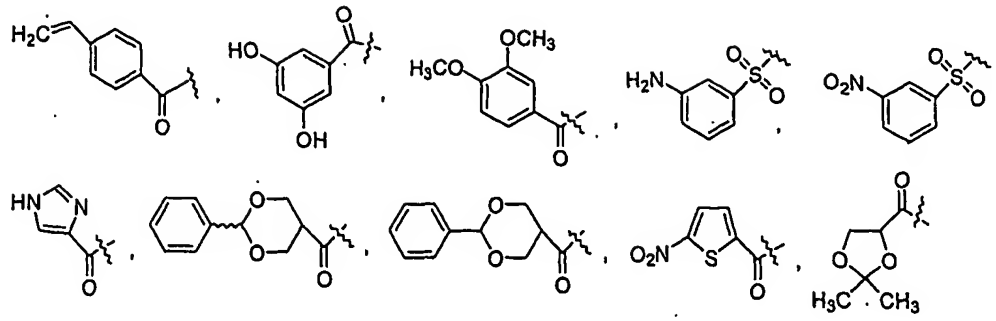


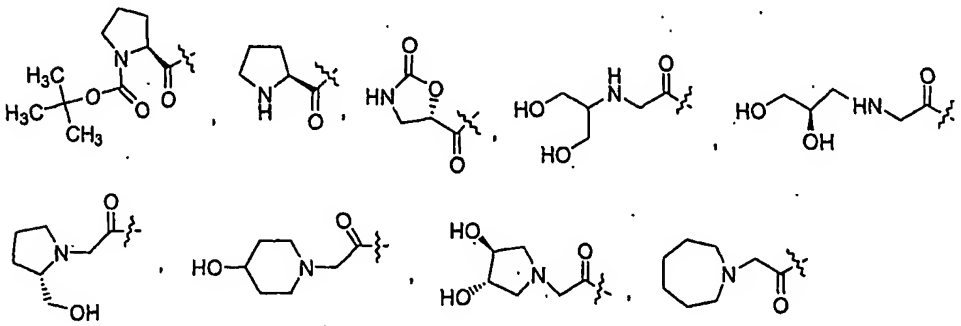
R^e=OH, OCH_3, CH_3, NH_2

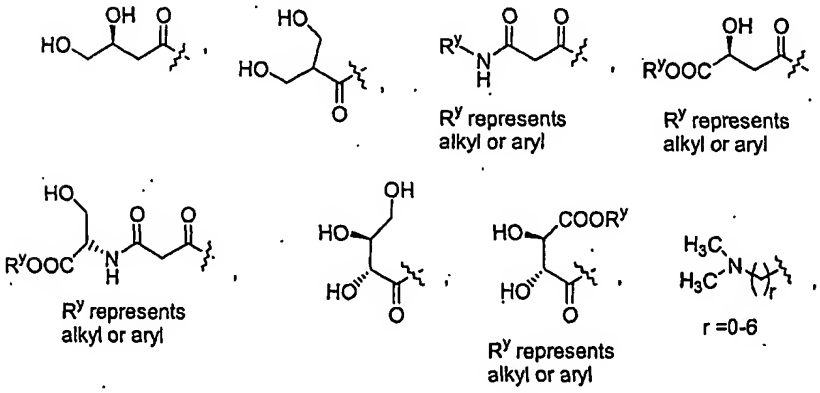


R^e=OH, OCH_3, CH_3, NH_2









R^y represents alkyl or aryl

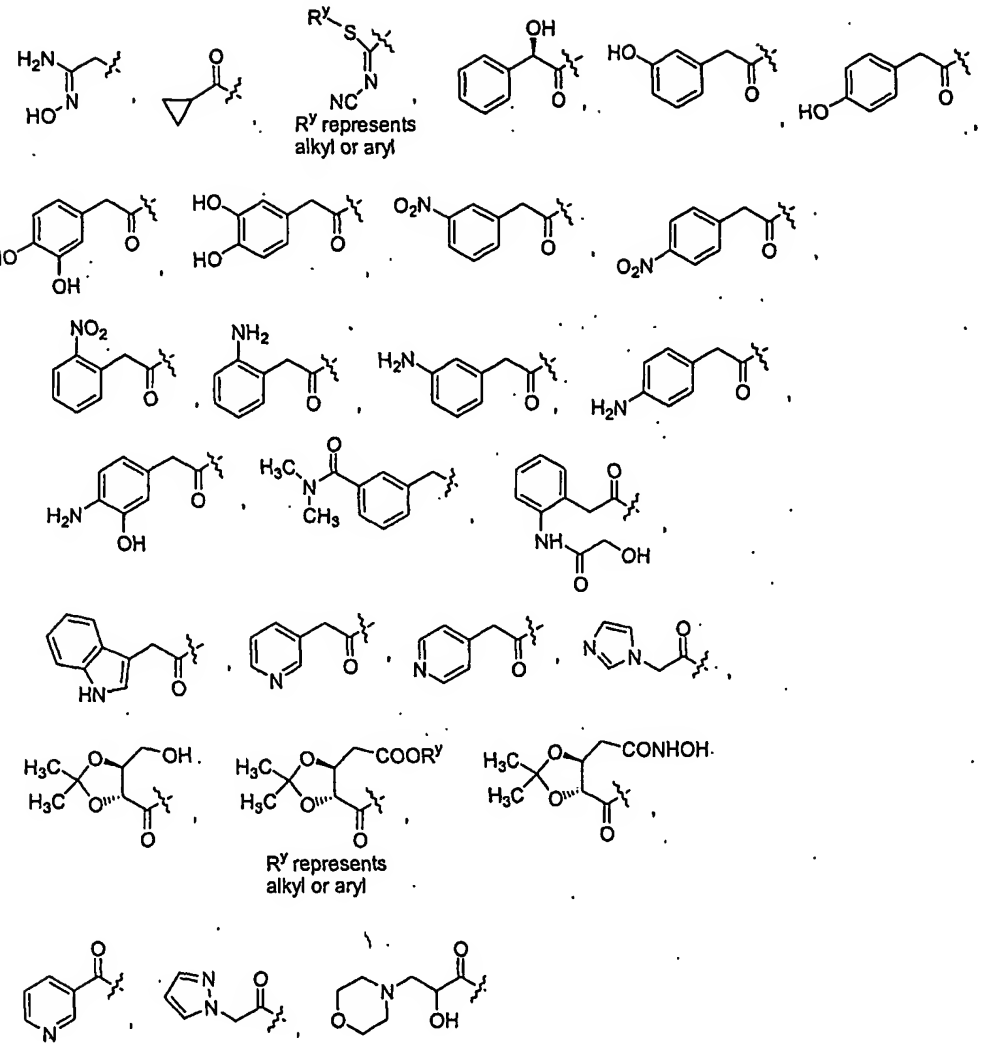
R^y represents alkyl or aryl

R^y represents alkyl or aryl

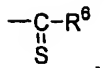
R^y represents alkyl or aryl

r =0-6

r =0-6


R^y represents alkyl or aryl
R^y represents alkyl or aryl

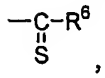
Another embodiment of compound of formula (Ia), where R_1 represents



, wherein R^6 represents alkyl or alkoxy group;

R^2 and R^3, which may be same or different, independently represent hydrogen or halogen;

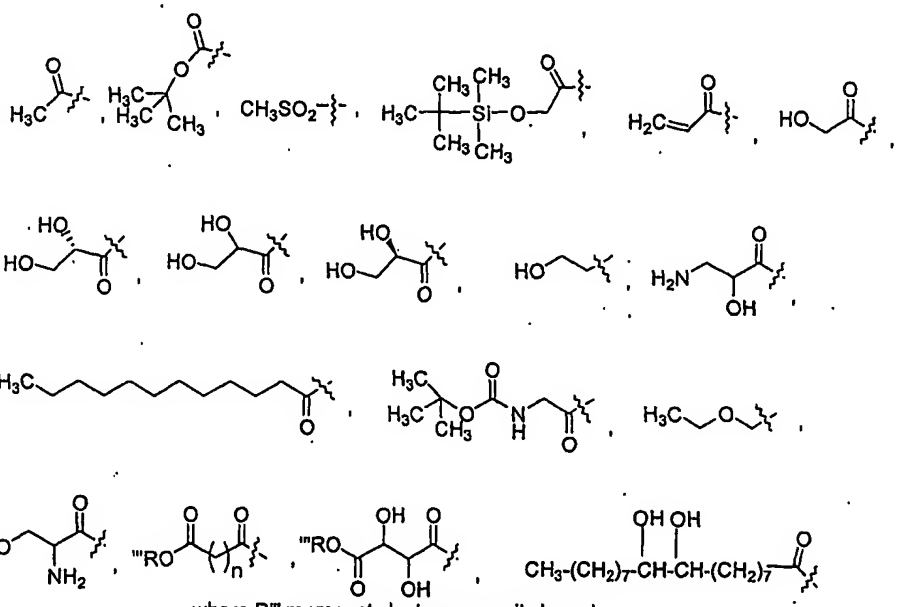
Another aspect of compound of formula (Ib), where R_1 represents



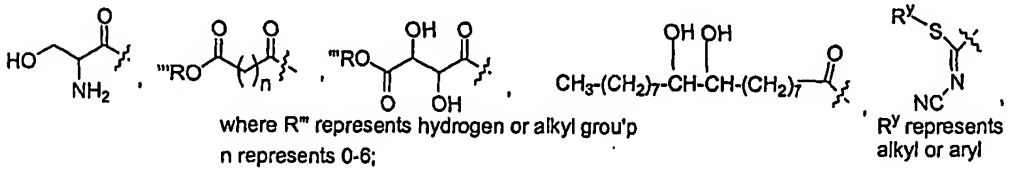
, wherein R^6 represents alkyl or alkoxy group;

R^2 and R^3, which may be same or different, independently represent hydrogen or halogen;

R^4 represents

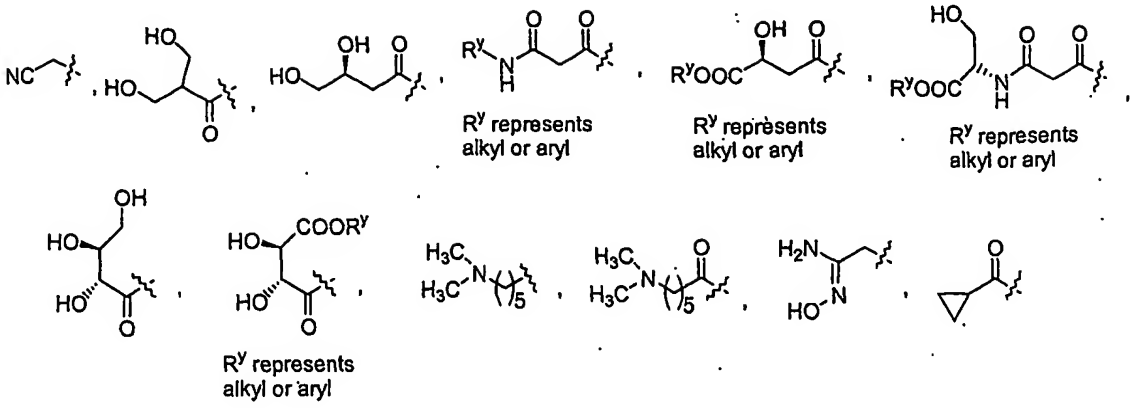
Hydrogen, Cyano, 

where R''' represents hydrogen or alkyl grou'p
n represents 0-6;

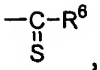


where R''' represents hydrogen or alkyl grou'p
n represents 0-6;

R^y represents alkyl or aryl

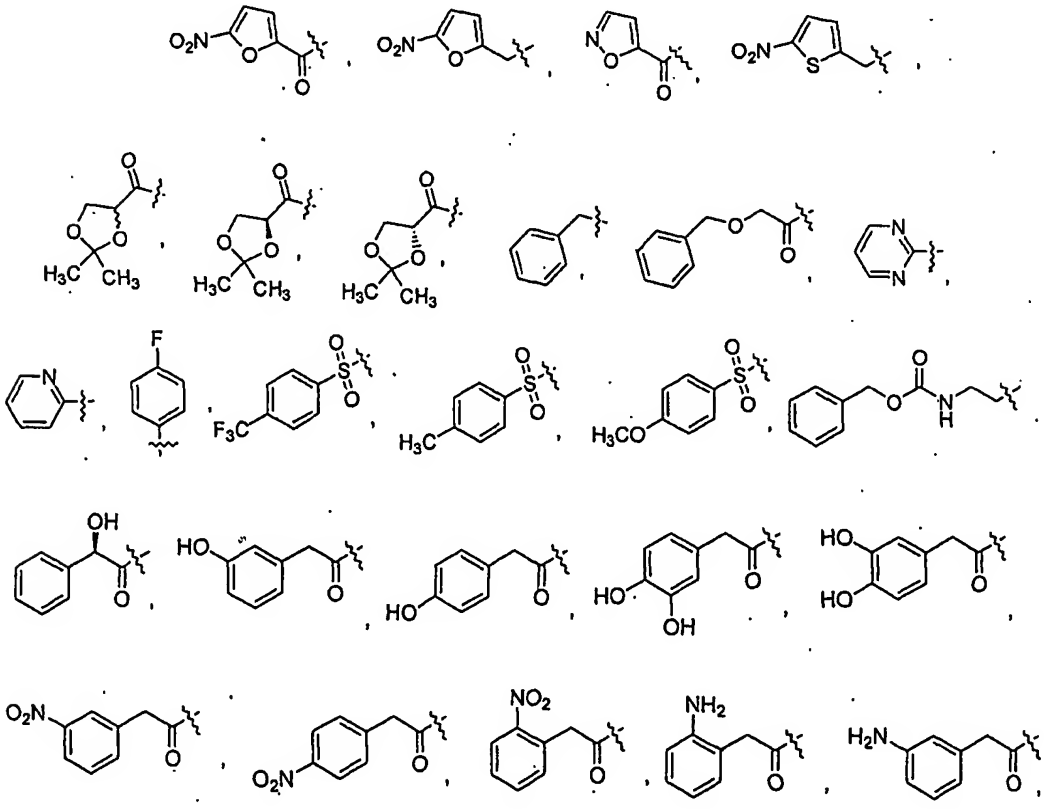


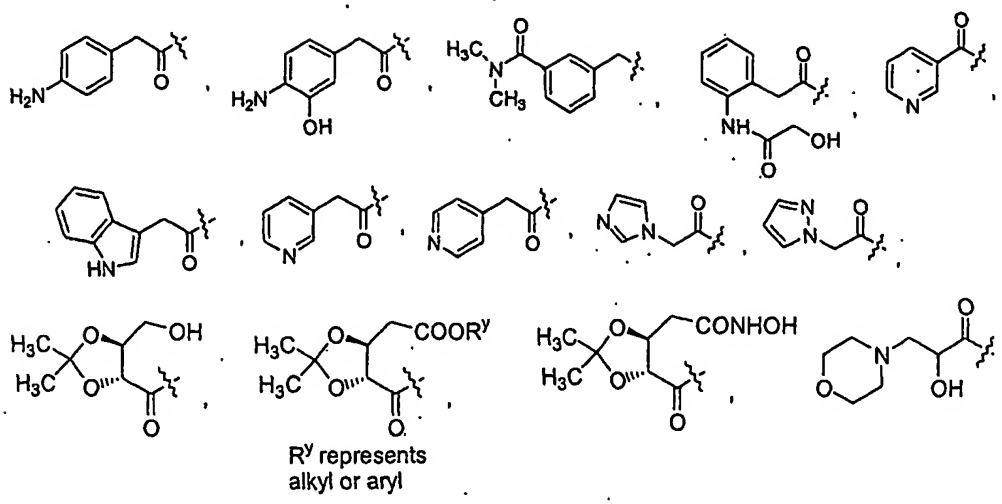
Another aspect of compound of formula (Ib), where R_1 represents


, wherein R^6 represents alkyl or alkoxy group;

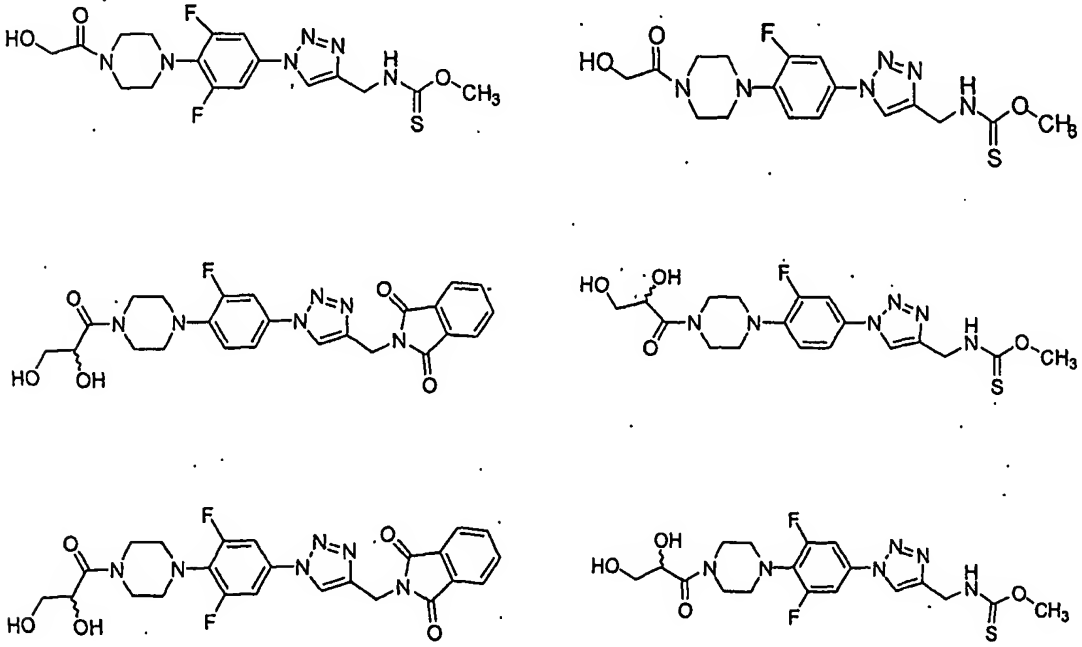
R^2 and R^3, which may be same or different, independently represent hydrogen or halogen;

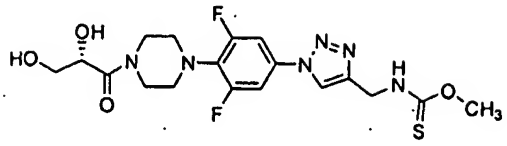
R^4 represents cyano,

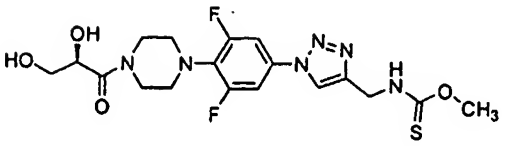


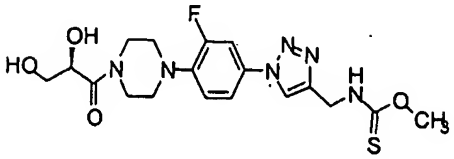


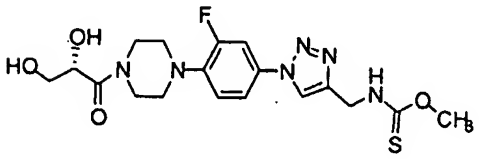
Another aspect of the present invention provides examples of formula (I), where '....' represents no bond and Z represents 'N' and all other symbols are as defined earlier have given in the following table:

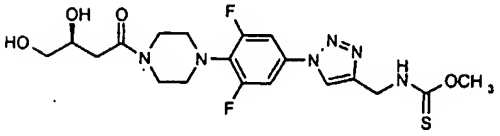


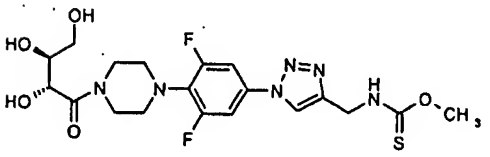


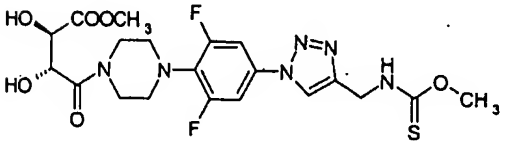


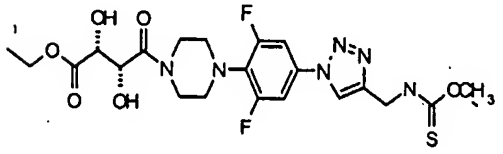


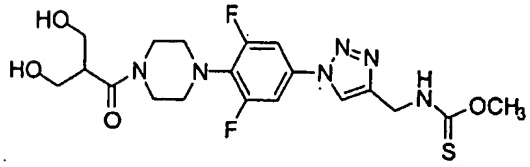


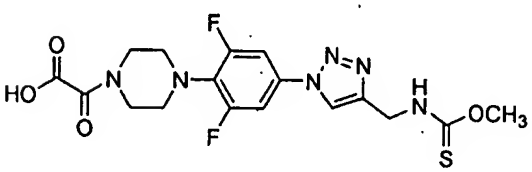


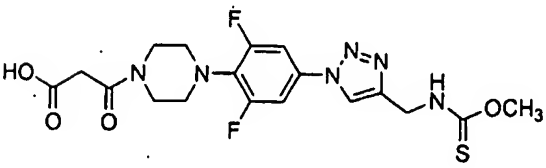


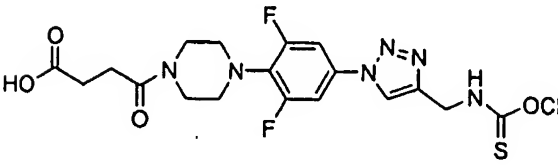


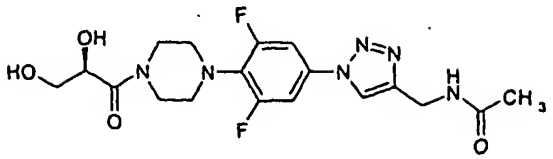
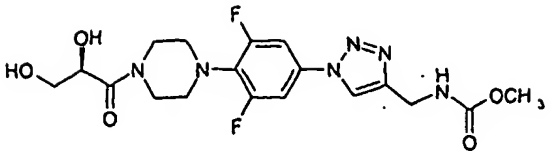
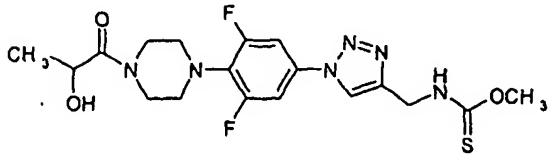
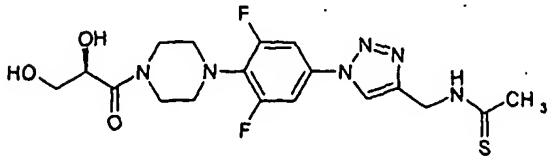
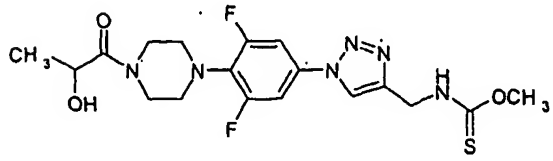
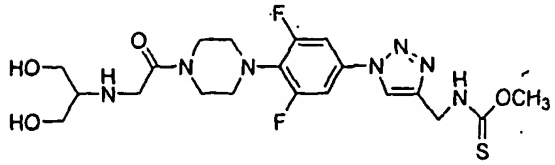
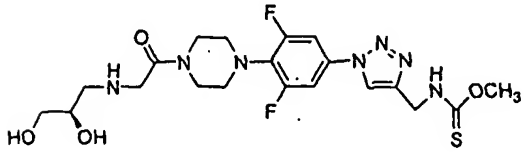






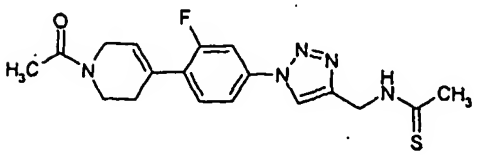
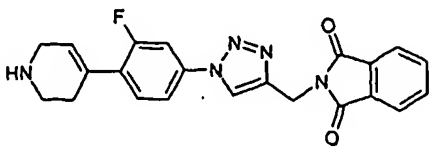


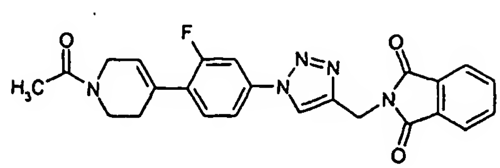


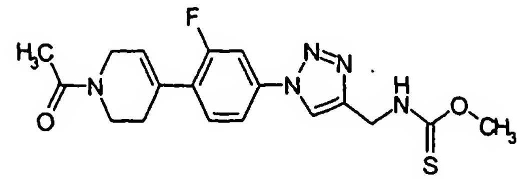








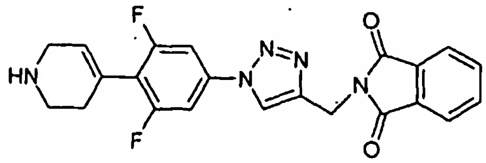
their stereoisomers and their pharmaceutically acceptable salts thereof;

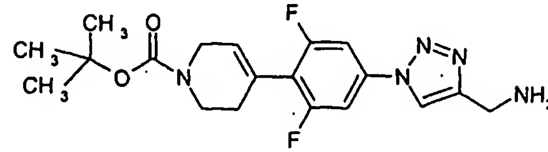
Another aspect of the present invention provides examples of formula (I), where '....' represents bond and Z represents 'C' and all other symbols are as defined earlier have given in the following table:

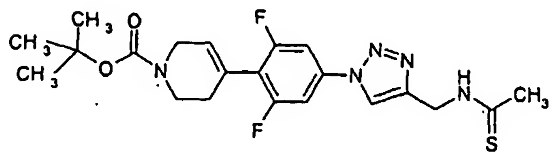



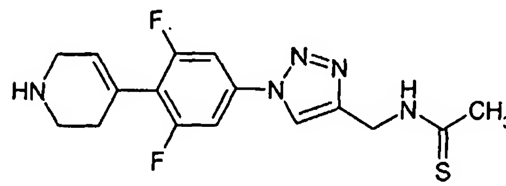


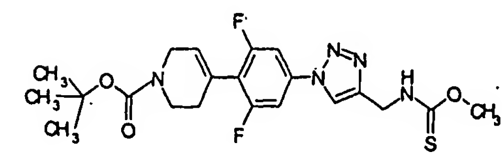


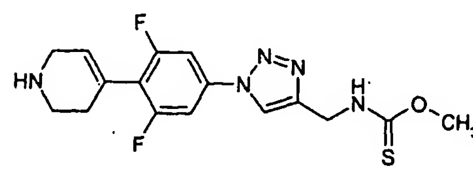


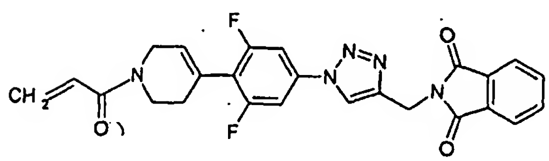


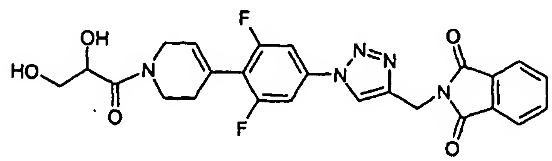


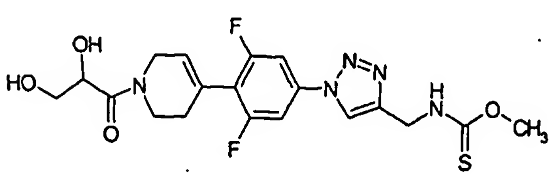


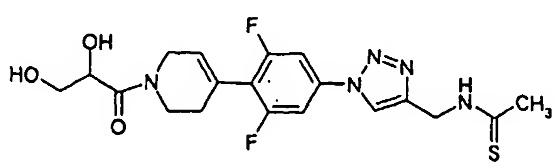


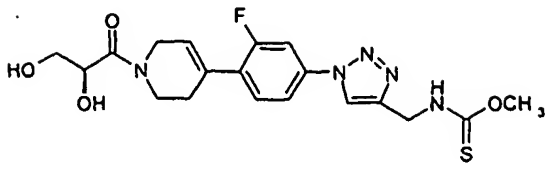
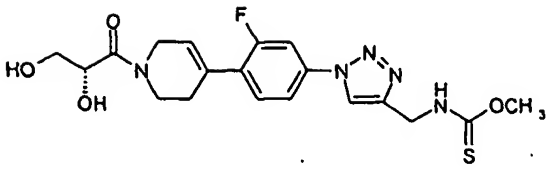
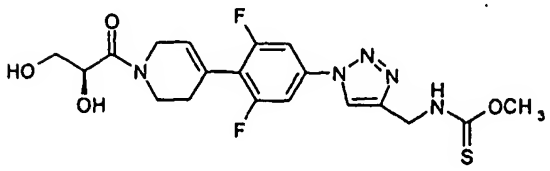
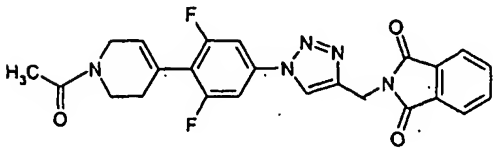
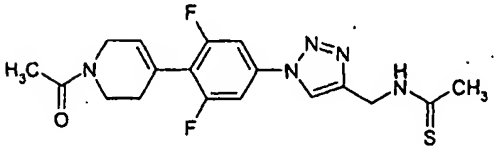
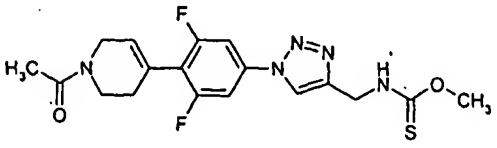
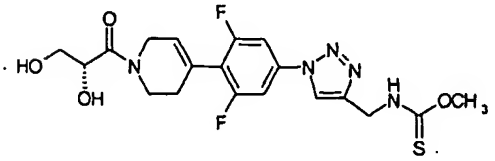
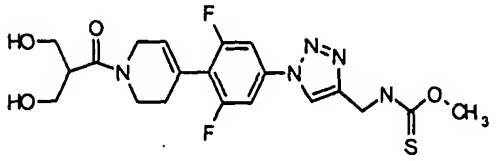






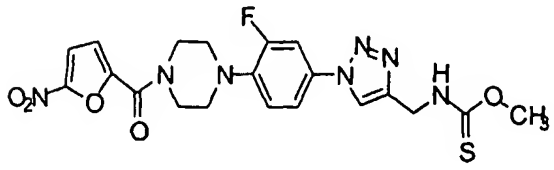
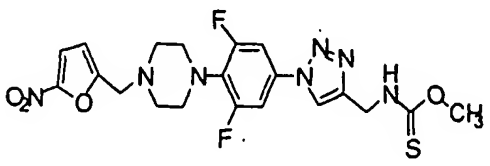


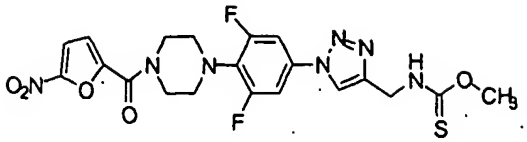


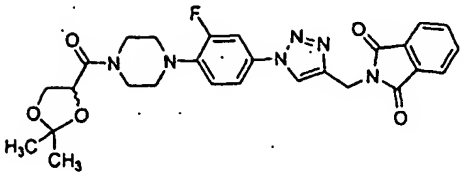









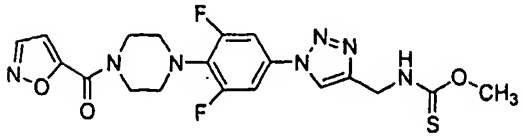
their stereoisomers and their prodrugs and their pharmaceutically acceptable salts thereof;

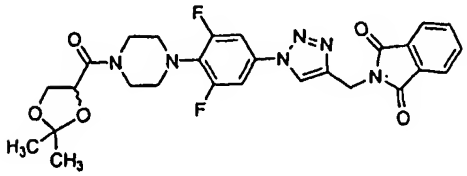
Another aspect of the present invention provides examples of formula (I), where '....' represents no bond and Z represents 'N' and all other symbols are as defined earlier have given in the following table:

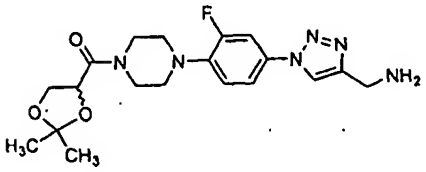



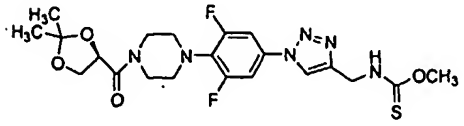


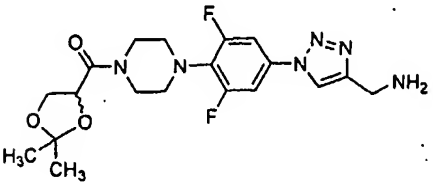


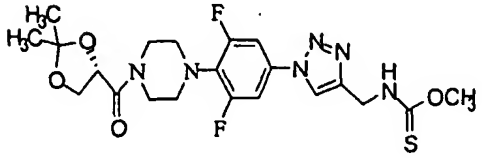


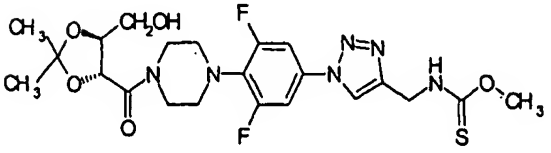


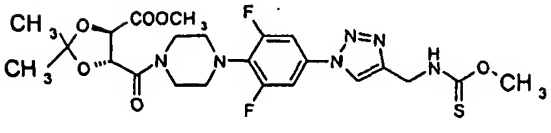


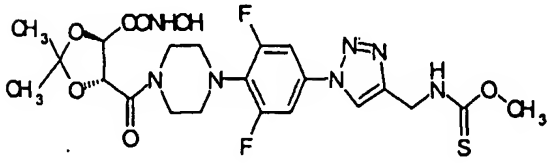


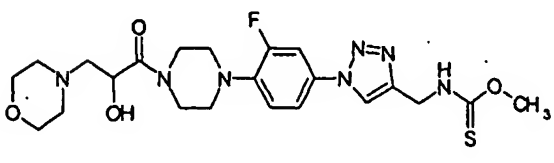


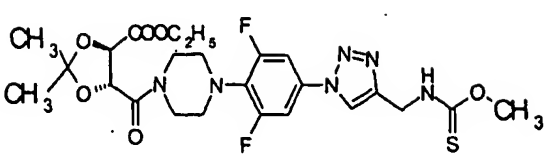


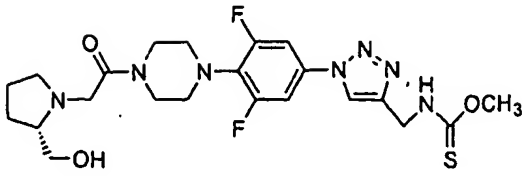


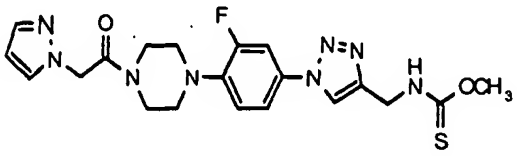


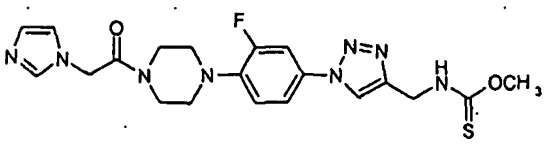


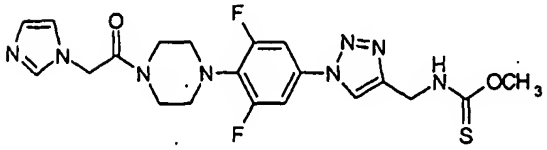


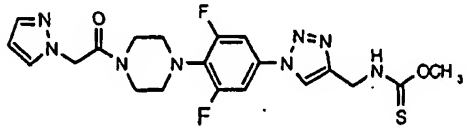


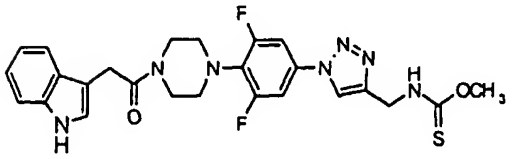


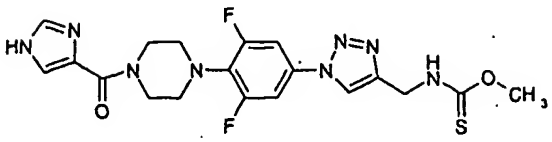


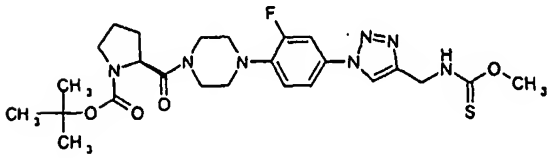






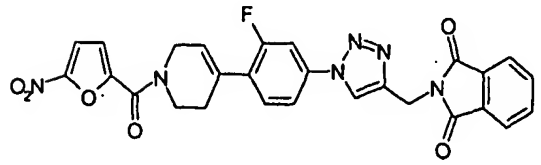


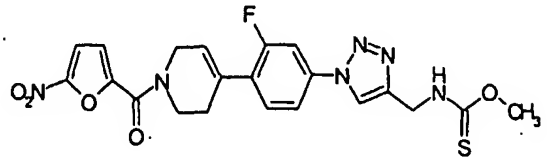


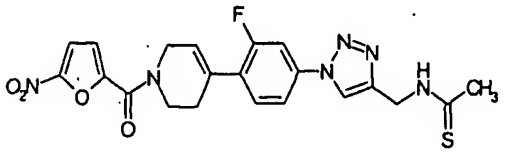


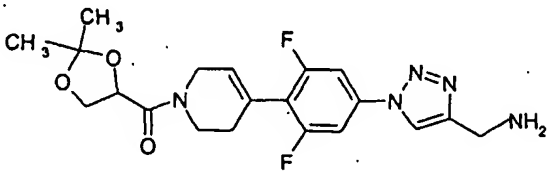
their stereoisomers and their pharmaceutically acceptable salts thereof;

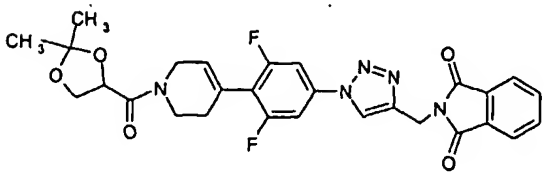
Another aspect of the present invention provides examples of formula (I), where '....' represents a bond and Z represents 'C' and all other symbols are as defined earlier have given in the following table:

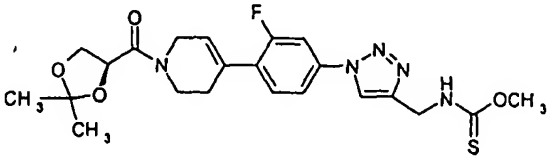


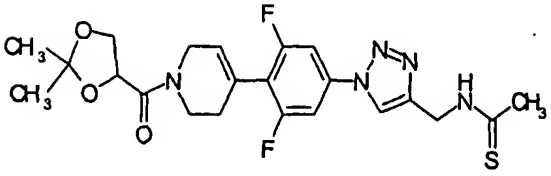


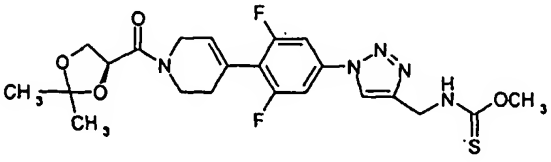


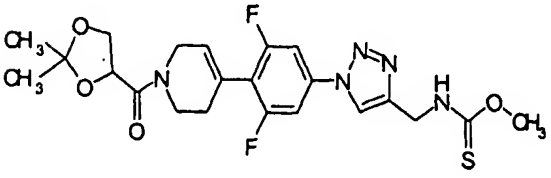


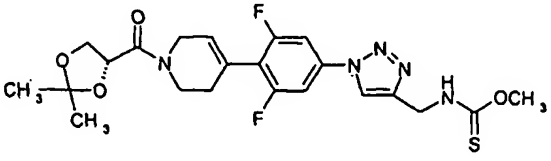


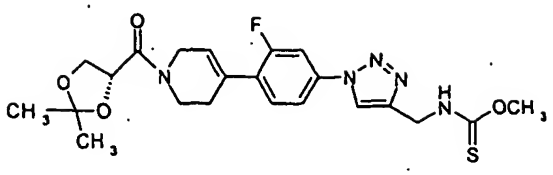
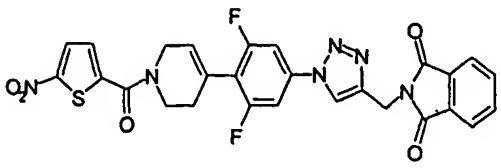
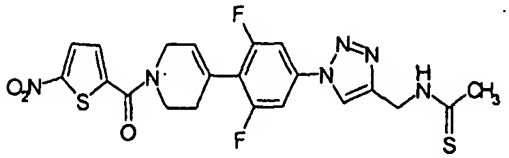
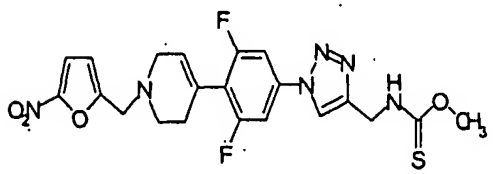
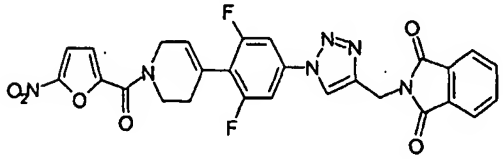
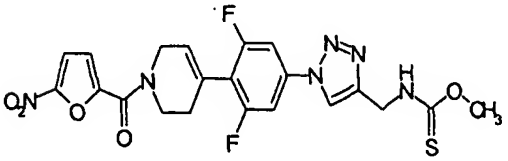
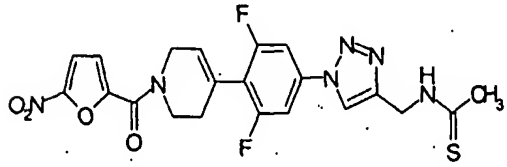
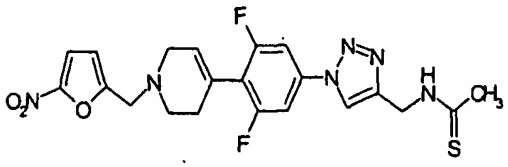


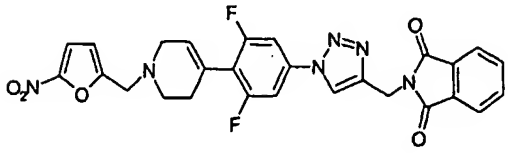










their stereoisomers and their pharmaceutically acceptable salts thereof;

Definitions:

'Halogen' is fluorine, chlorine, bromine, or iodine;

'Alkyl' group is optionally substituted linear or branched (C_1-C_{10}) alkyl group. Exemplary alkyl groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-pentyl, iso-pentyl, hexyl, heptyl, octyl and the like.

'Haloalkyl' group is optionally substituted linear or branched monohalo(C_1-C_{10})alkyl group, dihalo(C_1-C_{10})alkyl group, trihalo(C_1-C_{10})alkyl group, tetrahalo(C_1-C_{10})alkyl group, pentahalo(C_1-C_{10})alkyl group or hexahalo(C_1-C_{10})alkyl group. Exemplary alkyl groups include monohalomethyl, dihalomethyl, trihalomethyl, monohaloethyl, dihaloethylm trihaloehtylm tetrahaloethylm pentahaloethyl and the like.

'Hydroxyalkyl' group is linear or branched hydroxy (C_1-C_{10})alkyl group. Exemplary alkyl groups include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, hydroxyheptyl, hydroxyoctyl and the like.

'Hydroxyalkylamino' group is linear or branched hydroxy(C_1-C_{10})alkylamino group. Exemplary hydroxyalkylamino groups include hydroxymethylamino, hydroxyethylamino, hydroxypropylamino, hydroxybutylamino, hydroxypentylamino, hydroxyhexylamino, hydroxyheptylamino, hydroxyoctylamino and the like.

'Cycloalkyl' group is (C_3-C_8) cycloalkyl group. Exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

'Alkylamino' group represents monoalkylamino or dialkylamino group. 'Monoalkylamino' is (C_1-C_{10})alkylamino, where (C_1-C_{10})alkyl is as defined above. Exemplary monoalkylamino groups include methylamino, ethylamino, propylamino, isoporpylamino and the like. 'Dialkylamino' is di(C_1-C_{20})alkylamino, where (C_1-C_{10}) alkyl is as defined above. Exemplary dialkylamino groups include dimethylamino, diethylamino, ethylmethylamino and the like.

'Alkoxy' is (C_1-C_{10}) alkyl-O-, wherein the (C_1-C_{10}) alkyl group is as defined above. Exemplary alkyl groups include methoxy, ethoxy, propoxy, butoxy, iso-propoxy and the like.

'Cycloalkoxy' is (C_3-C_{10}) cycloalkoxy group. Exemplary cycloalkoxy groups include cyclopropoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy and the like.

'Alkenyl' is (C_2-C_{10}) alkenyl group. Exemplary alkenyl groups include ethenyl, propenyl, but-1-enyl, pentenyl, hexenyl and the like.

'Cycloalkenyl' is (C_3-C_{10})cycloalkenyl group. Exemplary cycloalkenyl groups include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl and the like.

'Alkylaminoalkyl' is (C_1-C_{10})alkylamino(C_1-C_{10})alkyl group, where alkyl group is as defined above. Exemplary alkylaminoalkyl groups include methylaminomethyl, methylaminoethyl, methylaminopropyl, methylaminobutyl, ethylaminomethyl, ethylaminoethyl, ethylaminopropyl, ethylaminobutyl, propylaminoethyl,

propylaminobutyl, butylaminopropyl, butylaminobutyl, propylaminomethyl, butylaminomethyl, ethylaminobutyl, propylaminopropyl and the like.

'Alkylcarbonyl' is (C_1-C_{10})alkylcarbonyl group. Exemplary alkylcarbonyl groups include methylcarbonyl, ethylcarbonyl, propylcarbonyl, isoporpynylcarbonyl, butylcarbonyl and the like.

'Alkenylcarbonyl' is (C_2-C_{10})alkenyl-CO, wherein (C_2-C_{10}) alkoxy is as defined above. Exemplary alkenycarbonyl groups include ethenylcarbonyl, propenylcarbonyl, butenylcarbonyl, but-1-enylcarbonyl and the like.

'Alkoxyalkyl' is (C_1-C_{10})alkoxy(C_1-C_{10})alkyl group, where alkoxy and alkyl groups are as defined above. Exemplary alkoxyalkyl groups include methoxymethyl, methoxyethyl, methoxypropyl, methoxypropyl, methoxybutyl, methoxypentyl, methoxyhexyl, ethoxymethyl, ethoxyethyl, ethoxypropyl, ethoxypropyl, ethoxybutyl, ethoxybutyl, ethoxypentyl, ethoxyhexyl, propoxyethyl, isopropoxyethyl, butoxyethyl, isobutoxyethyl and the like.

'Alkoxycarbonyl' is (C_1-C_{10}) alkoxycarbonyl, wherein (C_1-C_{10}) alkoxy is as defined above. Exemplary alkoxycarbonyl groups include methoxycarbonyl, ethoxycarbonyl and the like.

'Carboxyalkyl' is carboxy (C_1-C_{10})alkyl, where (C_1-C_{10})alkyl group is as defined above. Exemplary carboxyalkyl groups include carboxymethyl, carboxyethyl and the like.

'Alkylsulfonyl' is (C_1-C_{10})alkylsulfonyl, where (C_1-C_{10})alkyl group is as defined above. Exemplary alkylsulfonyl groups include methylsulfonyl, ethylsulfonyl and the like

'Alkylsulfinyl' is (C_1-C_{10})alkylsulfinyl, where (C_1-C_{10})alkyl group is as defined above. Exemplary alkylsulfinyl groups include methylsulfinyl, ethylsulfinyl and the like

'Alkylsulfanyl' is (C_1-C_{10})alkylsulfanyl, where (C_1-C_{10})alkyl group is as defined above. Exemplary alkylsulfanyl groups include methylsulfanyl, ethylsulfanyl and the like

'Alkylsulfonyloxy' is (C_1-C_{10}) alkylsulfonyloxy, where (C_1-C_{10})alkyl group is as defined above. Exemplary alkylsulfonyloxy groups include methylsulfonyloxy, ethylsulfonyloxy and the like.

'Aryl' is monocylic or polycyclic ring system of about 6 to 14 carbon atoms. Exemplary groups include phenyl, naphthyl and the like.

'Arylcarbonyl' is aryl-carbonyl group, where aryl group is as defined above.. Exemplary arylcarbonyl groups include phenylcarbonyl, naphthylcarbonyl and the like.

'Arylsulfonyl' is aryl-sulfonyl, where aryl group is as defined above. Exemplary arylsulfonyl groups include phenylsulfonyl, naphthylsulfonyl and the like.

'Arylsulfanyl' is aryl-sulfanyl, where aryl group is as defined above. Exemplary arylsulfanyl groups include phenylsulfanyl, naphthylsulfanyl and the like.

'Arylsulfinyl' is aryl-sulfinyl, where aryl group is as defined above. Exemplary arylsulfinyl groups include phenylsulfinyl, naphthylsulfinyl and the like.

'Alkylcarbonylaminoalkyl' is (C_1-C_{10})alkylcarbonylamino(C_1-C_{10})alkyl, where (C_1-C_{10})alkyl group is as defined above. Exemplary alkylcarbonylaminoalkyl groups include methylcarbonylaminomethyl, methylcarbonylaminoethyl and the like.

'Arylcarbonylaminoalkyl' is arylcarbonylamino (C_1-C_{10})alkyl, where aryl and (C_1-C_{10})alkyl group are as defined above. Exemplary arylcarbonylaminoalkyl include phenylcarbonylaminomethyl, phenylcarbonylaminoethyl and the like.

'Alkylcarbonyloxyalkyl' is (C_1-C_{10})alkylcarbonylamino(C_1-C_{10})alkyl, where (C_1-C_{10})alkyl group is as defined above. Exemplary alkylcarbonyloxyalkyl groups include methylcarbonyloxymethyl, ethylcarbonyloxymethyl and the like.

'Hydroxyalkylcarbonyl' is hydroxyl-(C_1-C_{10})alkylcarbonyl, where (C_1-C_{10})alkyl group is as defined above. Exemplary hydroxyalkylcarbonyl groups include hydroxymethylcarbonyl, hydroxyethylcarbonyl, hydroxypropylcarbonyl and the like.

'Aminoalkyl' is amino (C_1-C_{10})alkyl, where (C_1-C_{10})alkyl is as defined above. Exemplary amino alkyl groups include amino methyl, amino ethyl and the like.

'Arylamino' where aryl group is as defined above. Exemplary aryl amino groups include phenyl amino, naphthylamino and the like.

'Alkenyloxy' is (C_3-C_{10}) alkenyl-O-, where the (C_2-C_6) alkenyl group is as defined above. Exemplary alkenyl groups include ethenyloxy, propenyloxy, butenyloxy, pentenyloxy, hexenyloxy and the like.

'Acyl' is H-CO or (C_1-C_{20}) alkyl-CO- group, where (C_1-C_{20})alkyl is as defined above. Exemplary acyl groups include acetyl, propionyl, *iso*-propionyl, *tert*-butionyl and the like.

'Haloacyl' is Halogen-(C_1-C_{10}) alkyl-CO- group, where (C_1-C_{10})alkyl is as defined above. Exemplary haloacyl groups include haloacetyl, halopropionyl and the like.

'Acyloxy' is (C_1-C_{10}) acyl-O-, where acyl group is defined as H-CO- or (C_1-C_{10}) alkyl-CO-, where (C_1-C_{10}) alkyl group is as defined above. Exemplary acyl groups include acetyl, propionyl, and the like. Exemplary acyloxy groups include acetyloxy, propionyloxy, *iso*-propionyloxy, *tert*-butionyloxyand the like.

'Aryloxy' is optionally substituted aryl-O- group, where the aryl group is as defined above. Exemplary aryloxy groups include phenoxy, naphthyloxy and the like.

'Aralkyl' is aryl-(C_1-C_{10}) alkyl group, wherein aryl and (C_1-C_{10}) alkyl groups are as defined above. Exemplary aralkyl groups include benzyl, 2-phenylethyl and the like.

'Aralkylcarbonyl' is aralkyl-carbonyl group, wherein aralkyl group is as defined above. Exemplary aralkylcarbonyl groups include benzylcarbonyl, 2-phenylethylcarbonyl and the like.

'Aralkoxy' is aralkyl-O- group, wherein the aralkyl group as defined above. Exemplary aralkoxy groups include bezyloxy, 2-phenethyloxy and the like.

'Aralkoxyalkylcarbonyl' is aralkyl-O-(C_1-C_{10})alkyl-CO group, where aralkyl and (C_1-C_{10})alkyl groups are as defined above. Exemplary aralkoxyalkylcarbonyl groups include benzyloxymethylcarbonyl, benzyloxyethylcarbonyl, benzyloxypropylcarbonyl and the like.

'Heterocyclyl' is non-aromatic saturated monocyclic or polycyclic ring system of about 5 to about 10 carbon atoms, having at least one hetero atom selected from O, S or N. Exemplary heterocyclyl groups include aziridinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, oxazolidinyl, azepanyl, [1,3]-dioxanyl, 1,3-dioxolanyl, 1,4-dioxolanyl and the like.

'Heterocyclylcarbonyl' is heterocyclylcarbonyl, where heterocyclyl is as defined above. Exemplary heterocyclylcarbonyl groups include aziridinylcarbonyl, pyrrolidinylcarbonyl, piperidinylcarbonyl, piperazinylcarbonyl, morpholinylcarbonyl, thiomorpholinylcarbonyl, thiazolidinylcarbonyl, oxazolidinylcarbonyl, azepanylcarbonyl, [1,3]-dioxanylcarbonylcarbonyl, 1,3-dioxolanylcarbonyl, 1,4-dioxolanylcarbonyl and the like.

'Heterocyclylalkyl' is non-aromatic saturated monocyclic or polycyclic ring system of about 5 to about 10 carbon atoms, having at least one hetero atom selected from O, S or N. Exemplary heterocyclylalkyl groups include 4-ethylmorpholinyl, 4-propylmorpholinyl, 4-butylmorpholinyl, 4-pentylmorpholinyl, 4-ethyl-[1,3]dioxolanyl, 4-propyl-[1,3]dioxolanyl, 4-butyl-[1,3]dioxolanyl, 4-pentyl-[1,3]dioxolanyl, 5-ethyl-oxazolidinyl, 5-propyl-oxazolidinyl, 5-butyl-oxazolidinyl, 5-pentyl-oxazolidinyl, 1-ethyl-pyrrolidine, 1-propyl-pyrrolidine, 1-butyl-pyrrolidine, 1-pentyl-pyrrolidine, 2-ethyl-pyrrolidinyl, 2-propyl-pyrrolidinyl, 2-butyl-pyrrolidinyl, 2-pentyl-pyrrolidinyl, 5-ethyl-[1,3]dioxanyl, 5-propyl-[1,3]dioxanyl, 5-butyl-[1,3]dioxanyl, 1-ethyl-piperidyl, 1-propyl-piperidyl, 1-butyl-piperidyl, 1-pentyl-piperidyl, 1-ethyl-azepanyl, 1-propyl-azepanyl, 1-butyl-azepanyl, 1-pentyl-azepanyl and the like.

'Heteroaryl' is aromatic monocyclic or polycyclic ring system of about 5 to about 10 carbon atoms, having at least one heteroatom selected from O, S or N. Exemplary heteroaryl groups include as pyrazinyl, isothiazolyl, oxazolyl, isoxazolyl, 1H-pyrazolyl, pyrrolyl, pyridazinyl, thienopyrimidyl, furanyl, 1H-indolyl, isoindolyl, 1,3-benzodioxole, 1,3-benzoxathiole, quinazolinyl, pyridyl, thiophenyl and the like.

'Heteroarylcarbonyl' is heteroarylcarbonyl. Exemplary heteroarylcarbonyl groups include as pyrazinylcarbonyl, isothiazolylcarbonyl, oxazolylcarbonyl, isoxazolylcarbonyl, 1H-pyrazolylcarbonyl, pyrrolylcarbonyl, pyridazinylcarbonyl, thienopyrimidylcarbonyl, furanylcarbonyl, 1H-indolylcarbonyl, isoindolylcarbonyl, 1,3-benzodioxolecarbonyl, 1,3-benzoxathiolecarbonyl, quinazolinylcarbonyl, pyridylcarbonyl, thiophenylcarbonyl and the like.

'Heteroaralkyl' is heteroaryl-(C_1-C_{10}) alkyl group, wherein the heteroaryl and (C_1-C_{10}) alkyl groups are as defined above. Exemplary heteroaralkyl groups include 1-ethyl-1H-pyrazolyl, 1-propyl-1H-pyrazolyl, 1-butyl-1H-pyrazolyl, 1-pentyl-1H-pyrazolyl, 1-ethyl-1H-imidazolyl, 1-propyl-1H-imidazolyl, 1-butyl-1H-imidazolyl, 1-pentyl-1H-imidazolyl, 4-ethylpyridinyl, 4-propylpyridinyl, 4-butylpyridinyl, 4-pentylpyridinyl, 3-ethylpyridinyl, 3-propylpyridinyl, 3-butylpyridinyl, 3-pentylpyridinyl, 3-ethyl-1H-indolyl, 3-propyl-1H-indolyl, 3-butyl-1H-indolyl, 3-pentyl-1H-indolyl, 2-ethylfuranyl, 2-propylfuranyl, 2-butylfuranyl, 5-ethylisoxazolyl, 5-propylisoxazolyl, 5-butylisoxazolyl, and the like.

'Heteroaryloxy' is heteroaryl-O-, wherein the heteroaryl group is as defined above. Exemplary heteroaryloxy groups include pyrazinyloxy, isothiazolyloxy, oxazolyloxy, pyrazolyloxy, phthalazinyloxy, indolyloxy, quinazolinyloxy, pyridyloxy, thienyloxy and the like.

'Heteroaralkylcarbonyl' is heteroaralkyl-CO-group, where heteroaralkyl group is as defined above. Exemplary heteroaralkylcarbonyl groups include 1-ethyl-1H-pyrazolylcarbonyl, 1-propyl-1H-pyrazolylcarbonyl, 1-butyl-1H-pyrazolylcarbonyl, 1-pentyl-1H-pyrazolylcarbonyl, 1-ethyl-1H-imidazolylcarbonyl, 1-propyl-1H-imidazolylcarbonyl, 1-butyl-1H-imidazolylcarbonyl, 1-pentyl-1H-imidazolylcarbonyl, 4-ethylpyridinylcarbonyl, 4-propylpyridinylcarbonyl, 4-butylpyridinylcarbonyl, 4-pentylpyridinylcarbonyl, 3-ethylpyridinylcarbonyl, 3-propylpyridinylcarbonyl, 3-butylpyridinylcarbonyl, 3-pentylpyridinylcarbonyl, 3-ethyl-1H-indolylcarbonyl, 3-propyl-1H-indolylcarbonyl, 3-butyl-1H-indolylcarbonyl, 3-pentyl-1H-indolylcarbonyl,, 1,3-benzodioxolecarbonyl, 1,3-benzoxathiolecarbonyl, quinazolinylcarbonyl, pyridylcarbonyl,

2-ethylfuranylcarbonyl, 2-propylfuranylcarbonyl, 2-butylfuranylcarbonyl, 5-ethylisoxazolylcarbonyl, 5-propylisoxazolylcarbonyl, 5-butylisoxazolylcarbonyl, and the like.

'Heterocyclylalkylcarbonyl' is heterocyclyl-CO-group, where heterocyclylalkyl group is as defined above. Exemplary heterocyclylalkylcarbonyl groups include 4-ethylmorpholinylcarbonyl, 4-propylmorpholinylcarbonyl, 4-butylmorpholinylcarbonyl, 4-pentylmorpholinylcarbonyl, 4-ethyl-[1,3]dioxolanylcarbonyl, 4-propyl-[1,3]dioxolanylcarbonyl, 4-butyl-[1,3]dioxolanylcarbonyl, 4-pentyl-[1,3]dioxolanylcarbonyl, 5-ethyl-oxazolidinylcarbonyl, 5-propyl-oxazolidinylcarbonyl, 5-butyl-oxazolidinylcarbonyl, 5-pentyl-oxazolidinylcarbonyl, 1-ethyl-pyrrolidinylcarbonyl, 1-propyl-pyrrolidinylcarbonyl, 1-butyl-pyrrolidinylcarbonyl, 1-pentyl-pyrrolidinylcarbonyl, 2-ethyl-pyrrolidinylcarbonyl, 2-propyl-pyrrolidinylcarbonyl, 2-butyl-pyrrolidinylcarbonyl, 2-pentyl-pyrrolidinylcarbonyl, 5-ethyl-[1,3]dioxanylcarbonyl, 5-propyl-[1,3]dioxanylcarbonyl, 5-butyl-[1,3]dioxanylcarbonyl, 1-ethyl-piperidylcarbonyl, 1-propyl-piperidylcarbonyl, 1-butyl-piperidylcarbonyl, 1-pentyl-piperidylcarbonyl, 1-ethyl-azepanylcarbonyl, 1-propyl-azepanylcarbonyl, 1-butyl-azepanylcarbonyl, 1-pentyl-azepanylcarbonyl and the like.

'Heteroarylsulfonyl' is heteroaryl-sulfonyl group, Exemplary heteroarylsulfonyl groups include pyrazinylsulfonyl, isothiazolylsulfonyl, oxazolylsulfonyl, pyrazolylsulfonyl, pyrrolylsulfonyl, pyridazinylsulfonyl, thienopyrimidylsulfonyl, furylsulfonyl, indolylsulfonyl, isoindolylsulfonyl, quinazolinylsulfonyl, pyridylsulfonyl, thiophenylsulfonyl and the like.

'Carboxylic acid or its derivatives' may be amides or esters. Exemplary carboxylic acid groups include $CONH_2$, CONHMe, $CONMe_2$, CONHEt, $CONEt_2$, CONHPh, $COOCH_3$, $COOC_2H_5$ or $COOC_3H_7$.

'Phosphoric acid or its derivates' include $PO(OCH_3)_2$, $PO(OC_2H_5)_2$ and the like.

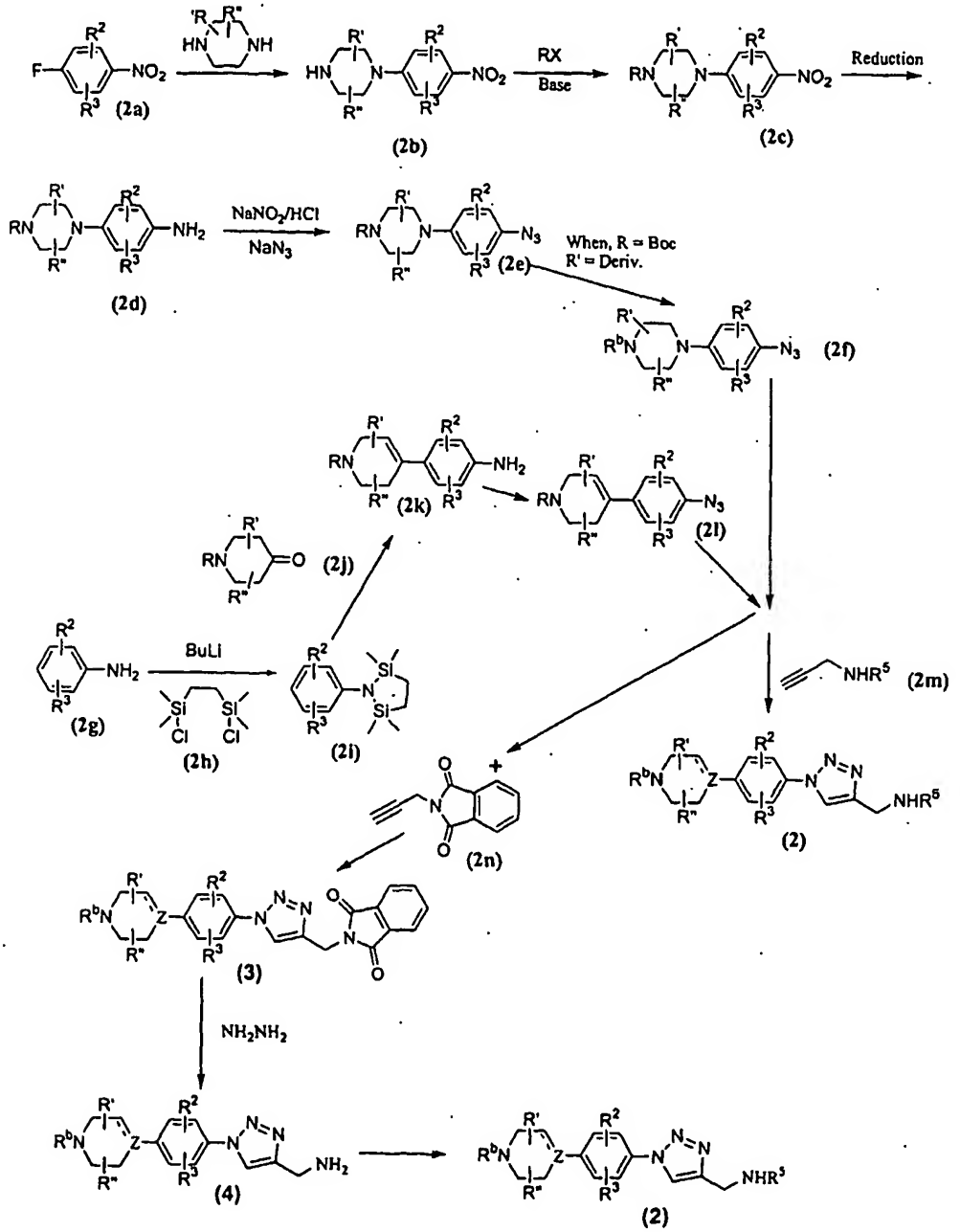
Another embodiment of the present invention provides a process for the preparation of compound of formula (I), Where R^b represents R or R^4, wherein R represents protecting group such as 't-butoxy carbonyl group (protecting group) and R^4 is as defined in description of compound of formula (I).

The compound of formula (2) represents compound of formula (I), when R^1 represents NHR^5, R^b represents R^4 and all other symbols are as defined in the description of compound of formula (I).

The compound of formula (2) represents compound of formula (I), when R^1 represents represents isoindole-1,3-dione, R^b represents R^4 and all other symbols are as defined in the description of compound of formula (I).

The compound of formula (2) represents compound of formula (I), when R^1 represents NHR^5 wherein R^5 represents hydrogen atom, R^b represents R^4 and all other symbols are as defined in the description of compound of formula (I).

which comprises:



The compound of formula (2a) and and piperazine were stirred in a suitable solvent selected from tetrahydrofuran (THF), dimethylformamide (DMF), chloroform, acetonitrile and the like. The temperature of the reaction was maintained in the range of 20 °C to boiling temperature of the solvent used in the reaction. After completion of the reaction the mixture was poured into cold water, and the mixture was cooled to ice temperature. The material was filtered and dried or can be extracted from aqueous layer with a solvent such as ethyl acetate, DCM, chloroform and the like.

The above compound of formula (2b) was converted to a compound of formula (2c) by using a solvent such as DMF, THF, 1,4-dioxane and the like, and *t*-butoxycarbonylanhydride [$(Boc)_2O$] in the presence of a base such as sodiumhydroxide (NaOH), potassiumhydroxide (KOH) and the like. The temperature of the reaction was maintained in the range of 0 to 50 °C, and the duration of the reaction is in the range of 0.5 to 5 hours. The resultant product was poured into water to obtain (*t*-butoxycarbonyl)'Boc' protected compound.

The compound of formula 2(c) was reduced to a compound of formula 2(d), by using a reducing agent such as palladium/carbon (Pd/C) or Platinum and hydrogen (H_2), sodium borohydrate/niclechloride ($NaBH_4/NiCl_2$) and the like. The solvent used in the reaction was selected from methanol, ethanol, propanol, isopropanol, ethyl acetate and the like.

The compound of formula (2d) was converted to a compound of formula (2e) by using sodium nitrite ($NaNO_2$) in the presence of hydrochloride (HCl) or acetic acid (CH_3COOH) followed by sodiumazide (NaN_3). The temperature of the reaction may be maintained in the range of about -40 °C to boiling temperature of the solvent used, preferably in the range of 0 °C to boiling temperature. The duration of the reaction may be in the range of about 0.5 to 15 hours, preferably in the range of about 0.5 to 5 hours

The compound of formula (2e) where R represents 'Boc' was first deprotected with dil. HCl or trifluoroacetic acid in a suitable solvent such as THF, 1,4-dioxane, chloroform and the like. The resultant mixture was neutralized by sodium carbonate, sodium bicarbonate and the like, followed by extraction with a solvent such as ethylacetate, dichloromethane, chloroform and the like to obtain a free amine. The free amine can be converted to suitable derivatives using conventional methods (eg: acid chloride / triethylamine).

The compound of formula (2g) is reacted with a compound of formula (2h), to obtain a compound of formula (2i), when X represents halogen atom, by using (C_1-C_{10})

alkyllithium such as methyllithium (MeLi), n-butyllithium (n-BuLi), secondary butyllithium (sec.BuLi), tertiary butyllithium (ter.BuLi) and the like. and the like. The compound of formula (Ic), where X represents hydrogen atom is obtained by treating with CsF. The solvent used in the reaction may be selected from tetrahydrofuran (THF), hexamethylphosphoramide (HMPA), diethylether and the like. The temperature and duration of the reaction can be maintained in the range of about -78 to about 100 °C and about 30 min to about 1.5 h respectively.

The compound of formula (2i) is reacted with a compound of formula (2j), by using a reagent (C_1-C_{10}) alkyllithium such as methyllithium (MeLi), n-butyllithium (n-BuLi), secondary butyllithium (sec.BuLi), tertiary butyllithium (ter.BuLi) and the like. The solvent used in the reaction may be selected from THF, hexametaphosphoric (HMPA), diethyl ether, 1,4-dioxane and the like. The temperature and duration of the reaction can be maintained in the range of about -78 to about 50 °C and about 4 to about 10 h respectively. The resultant compound was treated with any of the reagents selected from conc HCl, p-toluene sulfonic acid (p-TSA), mesyl chloride & triethylamine, 1,2-diazabicyclo[5,4,0]undec-7-ene (DBU), phosphorous oxychloride ($POCl_3$), The solvent used in the reaction is selected from pyridine, dichloromethane, acetonitrile, toluene and the like. The temperature and duration of the reaction can be maintained in the range of about 0 to about 150 °C and about 30 min to about 24 h respectively. The above obtained compound is converted to compound of formula (2k), where '....' represents no bond, by treating with Et_3SiH & $BF_3.OEt_2$, Et_3SiH & CF_3COOH, TMSCl, NaI, Me_2SiI_2, Bu_3SnH and the like, under the above reaction conditions.

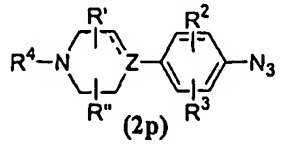
The compound of formula (2k) in dil. HCl, is reacted with $NaNO_2$ and NaN_3 or t-Butyl nitrile and NaN_3, to obtain a compound of formula (2l), The temperature and duration of the reaction can be maintained in the range of about 0 to about 150 °C and about 30 min to about 24 h respectively.

The compound of formula (2f) and/or (2l) was subjected to 1,3-dipolar cycloaddition with the corresponding acetylene derivative to obtain a compound of formula (2). The solvent used in the reaction was selected from DMF, acetonitrile, THF, toluene and the like. The reaction may be carried out in the presence of a catalyst such as CuI. The temperature of the reaction was maintained in the range of 0 to 90 °C. The duration of the reaction was maintained in the range of 0.5 to 6 hours. The compound of formula (2f) and/or (2k) was converted to a compound of formula (2) by adopting the similar procedure as described above.

The compound of formula (3) was converted to a compound of formula (4) by using reagents such as hydrazine, dialkylamine, ethylenediamine and the like. The solvents used in the reaction may be selected from methanol, ethanol, propanol, isopropanol and the like. The temperature was maintained in the range of 20 °C to the boiling temperature of the solvent used in the reaction. The duration of the reaction is in the range of 1 to 12 h.

The compound of formula (4) was converted to amide (where R^5 represents COR) by using the corresponding acid chloride and triethylamine or acid anhydride and base such as triethylamine, pyridine and the like. The resultant amide can be further converted to thioamide by using sulfur transfer reagent such as Lawesson's reagent or the amine can be converted to thiocyanate (NCS) by treating with thiophosgene and triethylamine, followed by refluxing in alcohol such as methanol, ethanol, propanol, isopropanol and the like.

The compound of formula (2f) (where protecting group is present on nitrogen atom of piperzine ring) and/or (2l) were also converted to a compound of formula (2p)



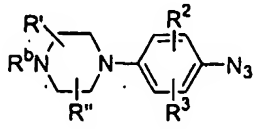
(2p)

The compound of formula (2f) and/or (2l), where R represents 'Boc' was first deprotected with chloroethylchloroformate, dil. HCl or trifluoroacetic acid in a suitable solvent such as dichloromethane, 1,2-dichloroethane, THF, 1,4-dioxane, chloroform and the like. The temperature of the reaction may be in the range of 0 to 40 °C. The duration of the reaction may be in the range of 0.5 to 12 hours. The resultant mixture was neutralized by sodium carbonate, sodium bicarbonate and the like, followed by extraction with a solvent such as ethylacetate, dichloromethane, chloroform and the like to obtain a free amine. The free amine can be converted to suitable derivatives using conventional methods (eg: acid chloride / triethylamine).

Alternatively, the deprotection can be carried out by using H_2/Pd-C, The solvent used may be selected from ethylacetate, methanol, ethanol, propanol and the like. The temperature of the reaction may be in the range of 0 to 40 °C. The duration of the reaction may be in the range of 0.5 to 12 hours.

The compound of formula 2(p) was converted to a compound of formulae or (5), by using the procedure as defined for the conversion of 2(f) and/or 2(l) to the compound of formulae (2) or (5).

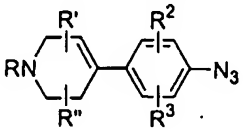
Another aspect of the present invention provides an intermediate of formula (2f)



(2f)

where R^b represents R or R^4 where R represents *tert*-butoxy carbonyl (BOC and all other symbols are as defined in the description of compounds of formula (I).

Another aspect of the present invention provides an intermediate of formula (2l)



(2l)

where R represents *tert*-butoxy carbonyl (BOC) and all other symbols are as defined in the description of compounds of formula (I).

It is appreciated that in any of the above-mentioned reactions, any reactive group in the substrate molecule may be protected according to conventional chemical practice. Suitable protecting groups in any of the above mentioned reactions are tertiarybutyldimethylsilyl, methoxymethyl, triphenyl methyl, benzyloxycarbonyl, tetrahydropyran(THP) etc, to protect hydroxyl or phenolic hydroxy group; N-tert-butoxycarbonyl (N-Boc), N-benzyloxycarbonyl (N-Cbz), N-9-fluorenyl methoxy carbonyl (-N-FMOC), benzophenoneimine, propargyloxy carbonyl (POC) etc, for protection of amino or anilino group, acetal protection for aldehyde, ketal protection for ketone and the like. The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected.

A method of treating or preventing an bacterial infections in a subject is provided by administering an therapeutically effective amount of compound of formula (I).

The term "therapeutically effective amount" shall mean that amount of a drug or

pharmaceutical agent that will elicit the biological or medical response of a tissue, system or patient that is being sought.

The pharmaceutically acceptable salts are prepared by reacting the compounds of formula (I) wherever applicable with 1 to 4 equivalents of a base such as sodium hydroxide, sodium methoxide, sodium hydride, potassium t-butoxide, calcium hydroxide, magnesium hydroxide and the like, in the presence of a solvent like ether, THF, methanol, t-butanol, dioxane, isopropanol, ethanol etc. Mixture of solvents may be used. Organic bases like lysine, arginine, diethanolamine, choline, tromethamine, guanidine and their derivatives etc. may also be used. Alternatively, acid addition salts wherever applicable are prepared by treatment with acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, p-toluenesulphonic acid, methanesulfonic acid, acetic acid, citric acid, maleic acid salicylic acid, hydroxynaphthoic acid, ascorbic acid, palmitic acid, succinic acid, benzoic acid, benzenesulfonic acid, tartaric acid and the like in the presence of a solvent like ethyl acetate, ether, alcohols, acetone, THF, dioxane etc. Mixture of solvent may also be used. The salts of amino acid groups and other groups may be prepared by reacting the compounds of formula (I) with the respective groups in the presence of a solvent like alcohols, ketones, ether etc. Mixture of solvents may be used.

The present invention also provides pharmaceutical compositions, containing compounds of the general formula (I), their pharmaceutically acceptable salts The pharmaceutical compositions according to this invention can be used for the treatment of bacterial infections. They can also be used for the treatment of bacterial infections associated with multidrug resistance. The pharmaceutical compositions according to this invention can also be administered prophylatically for the prevention of bacterial infections in a patient at risk of developing a bacterial infection.

The compounds alternatively be formulated and administered in a prodrug form. In general, prodrugs comprise functional derivatives of the claimed compounds which are capable of being enzymatically activated or converted into the more active parent form. Thus, in the treatment methods of the present invention, the term "administering" encompasses the treatment of the various disorders described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound in vivo after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in *Design of Prodrugs* (1985). *See also*, Wihnan, 14 *Biochem.*

Soc. Trans. 375-82 (1986); *Stella et al.*, Prodrugs: A Chemical Approach to Targeted Drug Delivery in *Directed Drug Delivery* 247-67 (1985).

The regioisomers of compound of formula (I) may be prepared by modifying the reaction conditions, use of reagents like acid to base or base to acid or by reaction with free base hydrazine instead of its salt with diketone. The molar proportion also can change the regioisomer formation.

The stereoisomers of the present invention include enatiomers such as (R), (S), a mixture of (R), (S), and mixture of (R) and (S). The individual optical isomers or required isomers may be obtained by using reagents in such a way to obtain single isomeric form in the process wherever applicable or by conducting the reaction in the presence of reagents or catalysts in their single enantiomeric form. Some of the preferred methods of resolution of racemic compounds include use of microbial resolution, resolving the diastereomeric salts formed with chiral acids such as mandelic acid, camphorsulfonic acid, tartaric acid, lactic acid, and the like wherever applicable or chiral bases such as brucine, cinchona alkaloids and their derivatives and the like. Commonly used methods are compiled by Jaques et al in "Enantiomers, Racemates and Resolution" (Wiley Interscience, 1981). Where appropriate the compounds of formula (I) may be resolved by treating with chiral amines, aminoacids, aminoalcohols derived from aminoacids; conventional reaction conditions may be employed to convert acid into an amide; the diastereomers may be separated either by fractional crystallization or chromatography and the stereoisomers of compound of formula (I) may be prepared by hydrolyzing the pure diastereomeric amide.

The pharmaceutical compositions may be in the forms normally employed, such as tablets, capsules, powders, dispersible granules, cachets, suppositories, syrups, solutions, suspensions and the like, may contain flavorants, sweeteners etc. in suitable solid or liquid carriers or diluents, or in suitable sterile media to form injectable solutions or suspensions. Such compositions typically contain from 0.5 to 90 % by weight of active compound, the remainder of the composition being pharmaceutically acceptable carriers, diluents or solvents.

Suitable pharmaceutically acceptable carriers include solid fillers or diluents and sterile aqueous or organic solutions. The active compounds will be present in such pharmaceutical compositions in the amounts sufficient to provide the desired dosage in the range as described above. Thus, for oral administration, the compounds can be combined with a suitable solid, liquid carrier or diluent to form capsules, tablets, powders, syrups, solutions, suspensions and the like. The pharmaceutical compositions, may, if

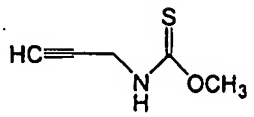
desired, contain additional components such as flavorants, sweeteners, excipients and the like. For parenteral administration, the compounds can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. For example, solutions in sesame or peanut oil, aqueous propylene glycol and the like can be used, as well as aqueous solutions of water-soluble pharmaceutically-acceptable acid addition salts or salts with base of the compounds. The injectable solutions prepared in this manner can then be administered intravenously, intraperitoneally, subcutaneously, or intramuscularly, with intramuscular administration being preferred in humans.

The compounds of the formula (I) or pharmaceutical compositions thereof as defined above are clinically administered to mammals, including human beings, via oral, parenteral and/or topical routes. Administration by the oral route is preferred, being more convenient and avoiding the possible pain and irritation of injection. However, in circumstances where the patient cannot swallow the medication, or absorption following oral administration is impaired, as by disease or other abnormality, it is essential that the drug be administered parenterally. By either route, the dosage is in the range of about 0.1 mg/kg to about 150 mg / kg, morepreferably about 3.0 mg/kg to about 100 mg/kg of body weight of the subject per day administered singly or as a divided dose. However, the optimum dosage whether for prevention or treatment for the individual subject being treated will be determined by the person responsible for treatment, Initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose may also be divided into multiple doses for administering, e.g. 2-6 times per day. It is to be understood that the dosages may vary depending upon the requirements of the patient, the severity of the bacterial infection being treated, and the particular compound being used. In a topical treatment an effective amount of compound of formula (I) is admixed in a pharmaceutically acceptable gel or cream vehicle that can be applied to the patient's skin at the area of treatment. Such creams and gels can be prepared by the procedures available in the literature and can include penetration enhancers.

The manner in which the compounds of this invention can be prepared is illustrated in the following examples, which demonstrate the preparation of typical species of the invention. In these examples, the identities of compounds, intermediates and final, were confirmed by infrared, nuclear magnetic spectral analyses as necessary. The examples are for the purpose of illustration only and should not be regarded as limiting the invention in any way.

Preparation 1:

Prop-2-ynyl-thiocarbamic acid O-methyl ester



To an ice cooled solution of propargyl amine (10 grams, 182 mmol) and triethyl amine (38 mL, 273 mmol) in tetrahydrofuran (THF) (300 mL) was added drop wise a solution of carbon disulfide (13.8 mL, 218 mmol) in THF (100 mL) through an addition funnel over a period of 0.5 hours. A solution of ethylchloroformate (17.4 mL, 182 mmol) in THF (100 mL) was then added drop wise to the reaction mixture. The cooling bath was removed and the reaction mixture was allowed to stir at 25-35 °C for 15 minutes. The precipitate formed was then filtered off and the filtrate was concentrated at 35 °C under reduced pressure. The resulting residue was diluted with methanol (200 mL) and the solution was refluxed for 2 hours. Evaporation of volatiles left a pasty mass, which was purified by passing through a silica gel column (petroleum ether/ethyl acetate, 1:9) to obtain the title compound as white solid (13.6 grams, 56%).

Melting Point: 67-68 °C

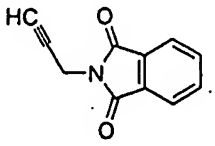
^{1}H NMR ($CDCl_3$): δ 6.65 & 6.30 (2 bs, 1H, rotamers in a ratio of 1:4), 4.35-4.25 (m, 2H), 4.04 & 3.96 (2s, 3H, rotamers in a ratio of 1:4), 2.25 (t, J = 2.4 Hz, 1H).

IR (KBr, cm^{-1}): 3237, 1542, 1214, 1148, 1074.

CI-MS (m/z): 130 (M^++1), 129, 114.

Preparation 2:

2-Prop-2-ynyl-isoindole-1,3-dione



A mixture of potassium phthalimide (10 grams, 54 mmol) and propargyl bromide (7.65 grams, 65 mmol) was heated in dimethyl formamide (DMF) (50 mL) at 80 °C for 8 hours. The reaction mixture was then poured into ice cold water. White solid obtained was filtered on a Buchner funnel and washed with water and dried (yield is 8.95 grams, 90%).

Melting Point: 138 °C .

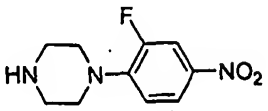
^{1}H NMR ($CDCl_3$): δ 7.95-7.85 (m, 2H), 7.75-7.68 (m, 2H), 4.46 (d, J = 2.5 Hz, 2H), 2.23 (t, J = 2.5 Hz, 1H).

IR (KBr, cm^{-1}): 3294, 2925, 1771, 1725, 1397.

CI-MS (m/z): 186 (M^++1), 148.

Preparation 3:

1-(2-Fluoro-4-nitro-phenyl)-piperazine



Piperazine (16.25 grams, 189 mmol) was added to a flask containing 3,4-difluoronitrobenzene (7 mL, 63 mmol) in acetonitrile (100 mL). The reaction mixture was refluxed for 2 hours. Acetonitrile was removed on rotavapor and the residue was diluted with water (30 mL) and extracted with ethyl acetate (3 x 150 mL). The combined organic layer was washed with water followed by brine and dried over sodium sulfate. Removal of volatiles yielded the title compound (12.8 grams, 90%).

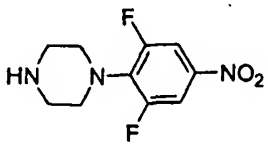
^{1}H NMR ($CDCl_3$): δ 8.01-7.92 (m, 2H), 7.02-6.91 (t, J = 8.8 Hz, 1H), 3.40-3.22 (m, 4H), 3.02-2.91 (m, 4H).

IR (KBr, cm^{-1}): 3438, 1330.

CI-MS (m/z): 226 (M^++1), 183.

Preparation 4:

1-(2, 6-Difluoro-4-nitro-phenyl)-piperazine



Title nitro compound (25.3 grams, 92%) was obtained from 3,4,5-trifuoronitrobenzene (20 grams, 113 mmol) and piperazine (29 grams, 339 mmol) by following the same procedure as descibed for the prepration of 1-(2-fluoro-4-nitro-phenyl)-piperazine, obtained in preparation 3.

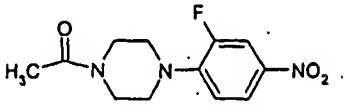
^{1}H NMR ($CDCl_3$): δ 7.76 (d, J = 10.0 Hz), 3.34 (bs, 4H), 3.02-2.97 (m, 4H)

IR (KBr, cm^{-1}): 3350, 3090, 2950, 2834, 2751, 1603, 1508, 1453, 1383, 1333, 1301, 1136, 1020, 779, 508.

CI-MS (m/z): 244 (M^++1), 228, 214, 196, 183, 155, 141, 112.

Preparation 5:

1-[4-(2-Fluoro-4-nitro-phenyl)-piperazin-1-yl]-ethanone



To a compound of 1-(2-fluoro-4-nitro-phenyl)-piperazine (2.0 grams, 8.9 mmol), obtained in preparation 3, and pyridine (1.9 mL, 17.8 mmol) was added acetic anhydride (10 mL, 106.8 mmol). The reaction mixture was stirred at 25-35 °C for 4 hours and then diluted with ice cold water. The precipitate formed was filtered through a Buchner funnel and dried under vacuum to get the title compound (2.24 grams, 94%).

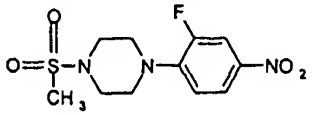
^{1}H NMR ($CDCl_3$): δ 8.00 (d, J = 4.9 Hz, 1H), 7.89 (d, J = 2.4 Hz, 1H), 6.92 (t, J = 8.7 Hz, 1H), 3.79 (t, J = 5.0 Hz, 2H), 3.65 (t, J = 5.0 Hz, 2H), 3.32-3.22 (m, 4H), 2.15 (s, 3H).

IR (KBr, cm^{-1}): 3440, 1949, 1337, 1240.

CI-MS (m/z): 268 (M^++1), 238, 204, 176, 144, 107, 97.

Preparation 6:

1-(2-Fluoro-4-nitro-phenyl)-4-methanesulfonyl-piperazine



To an ice cooled solution of 1-(2-fluoro-4-nitro-phenyl)-piperazine (2.0 grams, 8.9 mmol), obtained from preparation 3, in dichloromethane (40 mL) was added triethylamine (2.4 mL, 17.8 mmol) followed by the addition of methanesulfonyl chloride (1.02 mL, 13.35 mmol) at 0 °C. The reaction mixture was warmed to 25-35 °C and stirred for 2 hours. Concentration of the reaction mixture and addition of ice cooled water to the reaction mixture led to the precipitation of light yellow product. The precipitate was filtered through Buchner funnel and dried under vacuum to get the title compound (2.6 grams, 96%).

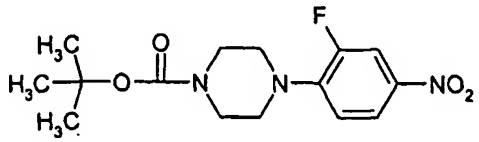
^{1}H NMR ($CDCl_3$): δ 8.02-7.87 (m, 2H), 7.05 (t, J = 8.8 Hz, 1H), 3.40 (bs, 4H), 2.88 (s, 4H).

IR (KBr, cm^{-1}): 3407, 3089, 2925, 2853, 1601, 1514, 1340, 1162, 958, 779, 521.

CI-MS (m/z): 304 (M^++1).

Preparation 7:

4-(2-Fluoro-4-nitro-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester



To an ice cooled solution of 1-(2-fluoro-4-nitro-phenyl)-piperazine (12.5 grams, 55.8 mmol), obtained in preparation 3, in 1,4-dioxane (108 mL) was added 1N sodium hydroxide (NaOH) solution (54 mL) followed by the addition of di-tert-butyl dicarbonate ($(BOC)_2O$) (14 mL, 61.38 mmol). The reaction mixture was allowed to come to 25-35 °C and stirred for 0.5 hour. It was then poured into ice cold water (200 mL) and the yellow precipitate formed was filtered through buchner funnel to get the desired compound (18.0 grams, 99%).

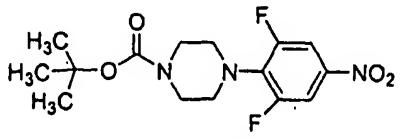
^{1}H NMR ($CDCl_3$): δ 8.01-7.88 (m, 2H), 6.93 (t, J = 8.6 Hz, 1H), 3.61 (t, J = 4.9 Hz, 4H), 3.24 (t, J = 4.9 Hz, 4H), 1.49 (s, 9H).

IR (KBr, cm^{-1}): 3119, 1692, 1605, 1512.

CI-MS (m/z): 326 (M^++1), 270, 240, 226, 195.183, 131, 96.

Preparation 8:

4-(2,6-Difluoro-4-nitro-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester:



Title compound (30.3 grams, 86%) was obtained from 1-(2,6-difluoro-4-nitro-phenyl)-piperazine (25 grams, 103 mmol), obtained in preparation 4, and $(Boc)_2O$ (26 mL, 113.2 mmol) following the same procedure as described for the preparation of 4-(2-fluoro-4-nitro-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (Preparation 7).

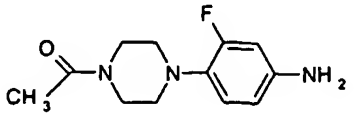
^{1}H NMR ($CDCl_3$): δ 6.56 (d, J = 9.6 Hz, 2H), 3.55-3.50 (m, 4H), 3.10- 3.00 (m, 4H), 1.58 (s, 9H).

IR (KBr, cm^{-1}) : 2121, 1695, 1501.

CI-MS: 340 (M++1), 314, 284, 258.

Preparation 9:

1-[4-(4-Amino-2-fluoro -phenyl)-piperazin-1-yl]-ethanone



To a solution of 1-[4-(2-fluoro-4-nitro-phenyl)-piperazin-1-yl]-ethanone (2.00 grams, 7.5 mmol), obtained in preparation 5, in a mixture of methanol and THF (4:1, 40 mL) was added ammonium formate (1.9 grams, 30 mmol) followed by the addition of 10% palladium on charcoal (Pd-C) (400 mg, 3.75 mmol) and stirred at 25-35 °C for 4 hours. The reaction mixture was filtered through a pad of celite and washed thoroughly with methanol. Removal of volatiles on a rotavapor left a pasty residue, which was diluted with water and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with brine and dried over sodium sulfate. Title amine was obtained after removal of volatiles (1.7 grams, 94%).

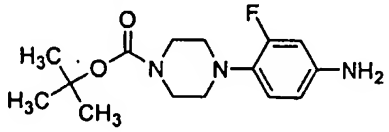
^{1}H NMR ($CDCl_3$): δ 6.86-6.76 (m, 1H), 6.49-6.41 (m, 2H), 3.81-3.77 (m, 2H), 3.66-3.61 (m, 2H), 2.98-2.93 (m, 4H), 2.16 (s, 3H).

IR (KBr, cm^{-1}): 3439, 3333, 3212, 2919, 1640, 1514, 1469.

CI-MS (m/z): 238 (M^++1), 220, 194, 165, 138, 124, 112.

Preparation 10:

4-(4-Amino-2-fluoro-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester:



To a solution of 4-(2-fluoro-4-nitro-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (9.00 grams, 27.7 mmol), obtained in preparation 7, in methanol and THF (4:1, 140 mL) was added ammonium formate (6.98 grams, 111 mmol) followed by the addition of 10% Pd-C (1.47 grams, 13.8 mmol) and stirred at 25-35 °C for 5 hours. The reaction mixture was filtered through a pad of celite and washed thoroughly with methanol. Removal of volatiles left a pasty mass, which was diluted with water and extracted with ethyl acetate (150 mL x 3). The combined organic layer was washed with water followed by brine and dried over sodium sulfate. Evaporation of solvent produced the title amine (7.75 grams, 95%).

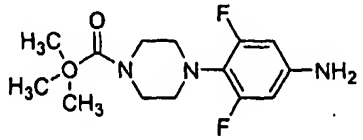
^{1}H NMR ($CDCl_3$): δ 6.78 (t, J = 9.1 Hz, 1H), 6.47-6.38 (m, 2H), 3.57 (t, J = 4.8 Hz, 4H), 2.90 (t, J = 4.8 Hz, 4H), 1.48 (s, 9H),

IR (KBr, cm^{-1}): 3451, 3347, 1681.

CI-MS (m/z): 296 (M^++1), 282, 240, 196.153, 106, 96.

Preparation 11:

4-(4-Amino-2, 6-difluoro-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester:



Title compound (20.5 grams, 75%) was prepared from 4-(2,6-difluoro-4-nitro-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (30 grams, 87.5 mmol), obtained in preparation 8, ammonium formate (22.06 grams, 349.8 mmol) and 10% Pd-C (4.68 grams, 4.4 mmol) following the same procedure as described for the preparation of 4-(4-amino-2-fluoro-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (Preparation 10).

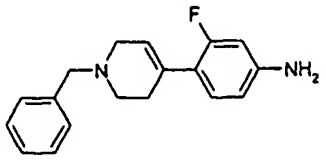
^{1}H NMR ($CDCl_3$): δ 6.16 (d, J = 10.5 Hz, 2H), 3.72 (bs, 2H), 3.53-3.48 (m, 4H), 3.02-2.97 (m, 4H), 1.48 (s, 9H).

IR (KBr, cm^{-1}): 3431, 3328, 2976, 2868, 1678, 1507, 1464, 1426, 1393, 1366, 1314, 1283, 1263, 1250, 1226, 1168, 1128, 1041, 1005, 958, 915, 837, 768, 734, 630, 579, 530.

CI-MS (m/z): 314 (M^++1), 258, 214, 115, 100.

Preparation 12:

4-(1-Benzyl-1, 2, 3, 6-tetrahydro-pyridin-4-yl)-3-fluoro-phenylamine



N-Butyllithium (62 mL, 1.6M in hexane) was added drop wise to a solution of 3-fluoroaniline (5 grams, 45.1 mmol) in dry THF (100 mL) at –78 °C under nitrogen atmosphere and stirred for 30 minutes. A solution of 1,2-bis (chlorodimethylsilyl)-ethane (10.65 grams, 49.54 mmol) in dry THF (100 mL) was then added. The reaction mixture was stirred at the same temperature for 45 minutes and then warmed to 25-35 °C. The

reaction mixture was quenched with water (60 mL) and then extracted with diethyl ether. The combined organic layers were dried over sodium sulphate. The solvent was removed under vacuum to obtain 1-(3-fluorophenyl)-2, 2, 5, 5-tetramethyl-[1, 2, 5] azadisilodine (11.4 grams) and this crude product was used in the next step without purification. To a solution of 1-(3-fluorophenyl)-2,2,5,5-tetramethyl-[1,2,5] azadisilodine (11.4 grams, 45.1 mmol) in dry THF (120 mL) at –78 °C was added sec-butyl lithium (41.6 mL, 1.3 M in cyclohexane / hexane(92 / 8), 54.1 mmol) slowly under nitrogen and allowed the reaction mixture to stir for 5 hours at the same temperature. A solution of N-benzyl-4-piperidone (9.36 grams, 49.5 mmol) in dry THF (100 mL) was added to the reaction mixture and allowed to rise to 25-35 °C and stirred for 12 hours. Brought the reaction mixture to 0 °C and acidified with concentrated hydrochloric acid (con.HCL). Washed the acidified reaction mixture with ether (2 x 100 mL). Then the reaction mixture was basified with 40% aqueous sodium hydroxide solution to litmus blue and extracted with diethyl ether (3 x 160 mL). Organic layer was dried over sodium sulphate and evaporated under vacuum to get a brown residue, which was mixed with conc. HCl (150 mL) and heated at 90 °C for 9 to 13 hours. Brought the reaction temperature down to 0 °C and basified with ammonia solution and extracted with dichloromethane (3 x 150 mL). Removed the solvent under reduced pressure and was purified by silica gel column chromatography (10% ethyl acetate/petroluem ether) to obtain 4-(1-benzyl-1, 2, 3, 6-tetrahydro-pyridin-4-yl)-3-fluoro-phenylamine as a brown solid (5.1 grams, 40%)

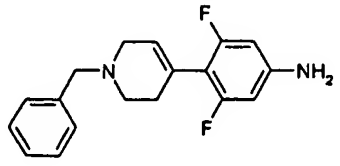
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.44-7.20 (m, 5H), 7.03 (t, J = 8.8 Hz, 1H), 6.44-6.22 (m, 2H), 5.96-5.78 (m, 1H), 3.63 (s, 2H), 3.92-3.40 (m, 2H), 3.22-3.16 (m, 2H), 2.80-2.58 (m, 2H), 2.58-2.40 (m, 2H)

IR (KBr): 3463, 3381, 3029, 2917, 2802, 1713, 1630, 1511, 1368, 1318, 1164 cm^{-1}

CI-MS (m/e): 283 (M^++1)

Preparation 13:

4-(1-Benzyl-1, 2, 3, 6-tetrahydro-pyridin-4-yl)-3, 5-difluoro-phenylamine



The title compound was prepared from 3,5-difluoroaniline (5 grams, 38.76 mmol) in 52% yield following the same procedure as described for the preparation of 4-(1-Benzyl-1, 2, 3, 6-tetrahydro-pyridin-4-yl)-3-fluoro-phenylamine (Preparation 12), in 52% yield.

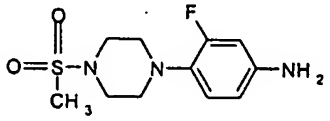
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.50-7.16 (m, 5H), 6.17 (d, J = 9.3 Hz, 2H), 5.82-5.67 (m, 1H), 4.00-3.70 (m, 2H), 3.62 (s, 2H), 3.22-3.02 (m, 2H), 2.82-2.60 (m, 2H), 2.50-2.30 (m, 2H)

IR (KBr): 3391, 2921, 1647, 1454, 1160, 1019, 829 cm^{-1}

CI-MS (m/e): (KBr): 301 (M+1)

Preparation 14:

3-Fluoro-4-(4-methanesulfonyl-piperazin-1-yl)-phenylamine



Title amine (1.7 grams, 94%) was prepared from 1-(2-fluoro-4-nitro-phenyl)-4-methanesulfonyl-piperazine (2.0 grams, 6.6 mmol), obtained from preparation 6, following the same procedure as described for the preparation of 1-[4-(4-amino-2-fluoro -phenyl)-piperazin-1-yl]-ethanone (Preparation 9)..

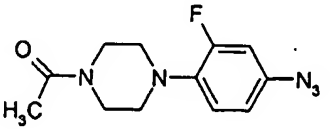
^{1}H NMR ($CDCl_3$): δ 6.81 (t, J = 9.0 Hz, 1H), 6.46-6.40 (m, 2H), 3.60 (bs, 4H), 3.39-3.36 (m, 2H), 3.09-3.07 (m, 2H), 2.83 (bs, 3H).

IR (KBr, cm^{-1}): 3451, 2922, 2852, 1633, 1316.

CI-MS (m/z): 274 (M^++1), 194.

Preparation 15:

1-[4-(4-Azido-2-fluoro -phenyl)-piperazin-1-yl]-ethanone



To an ice cooled solution of 1-[4-(4-amino-2-fluoro-phenyl)-piperazin-1-yl]-ethanone, (500 mg, 2.1 mmol), obtained in preparation 9, in 50% aquoes. HCl (2 mL) was added a saturated aqueous solution of sodium nitrite (291 mg, 4.21 mmol) drop wise. The reaction mixture was then allowed to come to 25-35 °C and stirred for 1 hour. A solution

of sodium acetate (3.5 grams, 42.2 mmol) and sodium azide (274 mg, 4.21 mmol) in water was added at 0 °C and stirred for 10 minutes. The precipitate formed was filtered through a Buchner funnel and dried under vacuum to get the title azide (360 mg, 65%).

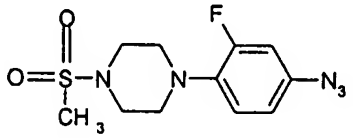
^{1}H NMR ($CDCl_3$): δ 6.94 (t, J = 8.8 Hz, 1H), 6.79-6.72 (m, 2H), 3.88-3.75 (m, 2H), 3.66-3.54 (m, 2H), 3.07-2.97 (m, 4H), 2.12 (s, 3H).

IR (KBr, cm^{-1}): 3322, 2925, 2117, 1233, 1101, 758.

CI-MS (m/z): 264 (M^++1), 252, 237, 235, 223, 210, 196.

Preparation 16:

3-Fluoro-4-(4-methanesulfonyl-piperazin-1-yl)-phenylazide



Title azide (975 mg, 89%) was obtained from 3-fluoro-4-(4-methanesulfonyl-piperazin-1-yl)-phenylamine (1.0 gram, 3.66 mmol), obtained from preparation 14, following the same procedure as described for the preparation of 1-[4-(4-Azido-2-fluoro -phenyl)-piperazin-1-yl]-ethanone (Preparation 15)

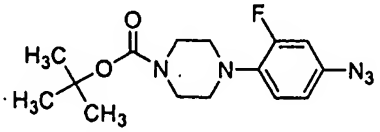
^{1}H NMR ($CDCl_3$): δ 6.93-6.89 (m, 1H), 6.79-6.72 (m, 2H), 3.40-3.37 (m, 4H), 3.16-3.12 (m, 4H), 2.83 (s, 3H).

IR (KBr, cm^{-1}): 3423, 2929, 2840, 2124, 1507, 1326, 1154, 524.

CI-MS (m/z): 300 (M^++1), 271.

Preparation 17:

4-(4-Azido-2-fluoro-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester



Sodium azide (1.32 grams, 20.34 mmol), moist with water (1 mL) was suspended in *tert*-butyl alcohol (25 mL) followed by the addition of 4-(4-amino-2-fluoro-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (2.0 grams, 6.78 mmol), obtained in preparation 10, and *tert*-butyl nitrite[1] (16 mL, 81 mmol) and heated at 70 °C for 3 hours. The reaction mixture was then diluted with water, extracted with ethyl acetate (2×100 mL) and the combined organic layer was washed with brine and dried over sodium sulfate. Removal of volatiles under reduced pressure and chromatographic purification of

the residue over silica gel (5:95 ethyl acetate/petroleum ether) afforded the title azide (1.5 grams, 70 %).

1. Vogel's Textbook of Practical Organic Chemistry, 5th Ed., 1989, Longman, UK.

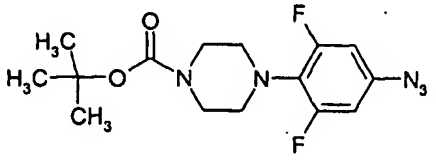
^{1}H NMR ($CDCl_3$): δ 6.93-6.84 (m, 2H), 6.70 (d, J = 4.4 Hz, 1H), 3.59-3.54 (m, 4H), 2.98-2.93 (m, 4H), 1.57 (s, 9H).

IR (KBr, cm^{-1}): 2977, 2113, 1699, 1507, 1421, 1231, 1189, 908.

CI-MS (m/z): 322 (M^++1), 308, 293, 266, 237.

Preparation 18:

4-(4-Azido-2, 6-difluoro-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester:



Title compound (15.6 grams, 72%) was prepared from 4-(4-amino-2,6-difluoro-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (20 grams, 63.9 mmol), obtained in preparation 11, and 10% aqueous.HCl, sodium nitrate (8.82 grams, 127.8 mmol), sodium azide (8.31 grams, 127.8 mmol) and sodium acetate (174 grams, 1278 mmol) following the same procedure as described for the preparation of 1-[4-(4-azido-2-fluoro-phenyl)-piperazine-1-yl]-ethanone (Preparation 15).

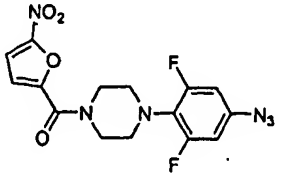
^{1}H NMR ($CDCl_3$): δ (d, J = 9.52 Hz, 2H), 3.53 (t, J = 4.88 & 5.13 Hz, 4H), 3.10-3.08 (m, 4H).

IR (KBr, cm^{-1}): 3445, 2969, 2943, 2860, 2124, 1694, 1626, 1572, 1500, 1459, 1427, 1366, 1317, 1283, 1250, 1169, 1133, 1073, 1041, 998, 968, 910, 887, 841, 764, 735, 619, 519.

MS (m/z): 340 (M^++1), 314, 284, 258, 240, 186, 149, 121, 97.

Preparation 19:

[4-(4-Azido-2, 6-difluoro phenyl)-piperazin-1-yl]-(5-nitro-furan-2-yl)-methanone



To an ice cooled solution of 4-(4-azido-2,6-difluoro-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (1.0 grams, 2.95 mmol), obtained from preparation 18, was

added trifluoroacetic acid (4 mL) and stirred at the same temperature for 1 hour. Excess of trifluoroacetic acid was removed on rotavapor and the resulting salt was washed with petroleum ether and dried under vacuum. To the solution of the above salt in dichloromethane (15 mL) was added triethylamine (1.23 mL, 8.85 mmol) at 0 °C followed by the addition of 5-nitrofuroyl chloride (520 mg, 2.95 mmol). The reaction mixture was then allowed to stir 9 to 13 hours at 25-35 °C. Water was added to the reaction mixture and extracted with ethyl acetate (3 x 30 mL). The combined organic portion was washed with water followed by brine and dried over sodium sulfate. The residue obtained upon concentration was purified by column chromatography (60-120 mesh silica gel, 1:4, and ethyl acetate/pet ether) to obtain the title compound (500 mg, 45%).

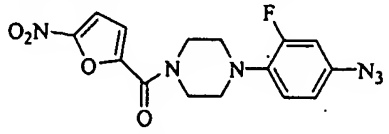
^{1}H NMR ($CDCl_3$): δ 7.38 (d, J = 3.9 Hz, 1H), 7.23 (d, J = 3.4 Hz, 1H), 6.60 (d, J = 9.3 Hz, 2H), 3.96 (bs, 4H), 3.26 (bs, 4H).

IR (KBr, cm^{-1}): 3436, 3139, 3109, 2923, 2851, 2122, 1633, 1577, 1512, 1434, 1388, 1356, 1329, 1275, 1242, 1025, 973, 921, 838, 759, 607, 527, 497.

CI-MS (m/z): 379 (M^++1), 351, 252, 210, 154, 140.

Preparation 20:

[4-(4-Azido-2-fluoro-phenyl)-piperazin-1-yl]-(5-nitro-furan-2-yl)-methanone



The title compound was prepared from 4-[(4-azido-2-fluoro-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester and 5-nitro-furoyl chloride, obtained in preparation 17, following the same procedure as described for the preparation of [4-(4-azido-2,6-difluoro-phenyl)-piperazin-1-yl]-(5-nitro-furan-2-yl)-methanone (Preparation 19).

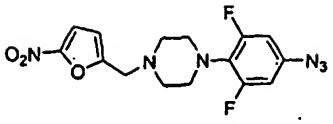
^{1}H NMR ($CDCl_3$) : δ 7.34-7.21 (m, 2H), 6.91 (t, J = 8.8 Hz, 1H),6.76-6.70 (m, 1H), 6.37 (bs, 1H), 4.15-3.91 (m, 4H), 3.12 (bs, 4H).

IR (KBr, cm^{-1}) : 2925, 2855, 2130, 1634, 1529, 1508.

CI-MS : 361 (M^++1), 333, 320, 205.

Preparation 21:

1-(4-Azido-2, 6-difluoro-phenyl)-4-(5-nitro-furan-2-ylmethyl)-pipearazine:



The title compound was prepared from 4-[(4-azido-2-fluoro-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (827 mg, 65%) and 5-nitro furyl mesylate (771.3 mg, 3.49 mmol) by following the same procedure as described for the preparation of [4-(4-azido-2,6-difluoro-phenyl)-piperazin-1-yl]-(5-nitro-furan-2-yl)-methanone (Preparation 19).

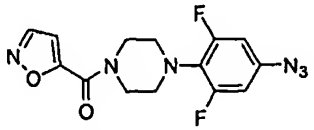
^{1}H NMR ($CDCl_3$): δ 7.29 - 7.25 (m, 1H), 6.58 – 6.48 (m, 3H), 3.68 (s, 2H), 3.17 (bs, 4H), 2.81 (bs, 4H).

IR (KBr, cm^{-1}): 2831, 2115, 1629, 1573, 1501, 1443, 1389, 1357, 1236, 1137, 1028, 969, 928, 812, 739, 611.

CI-MS (m/z): 365 (M^++1), 348, 337, 318, 250.

Preparation 22:

[4-(4-Azido-2,6-difluoro-phenyl)-pipearazin-1-yl]-isoxazol-5-yl-methanone:



The title compound was prepared from 4-[(4-azido-2-fluoro-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (520 mg, 75.3%) and isoxazole carbonyl chloride (271 mg, 2.06 mmol), following the same procedure as described for the preparation of [4-(4-azido-2, 6-difluoro phenyl)-piperazin-1-yl]-(5-nitro-furan-2-yl)-methanone (Preparation 19).

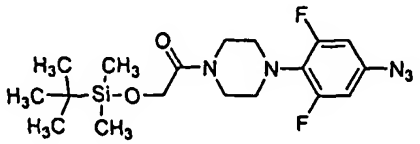
^{1}H NMR ($CDCl_3$): δ 8.34 (s, 1H), 6.84 (s, 1H), 6.58 (d, J = 9.3 Hz, 2H), 3.88 (bs, 4H). 3.23 (bs, 4H).

IR (KBr, cm^{-1}): 3118, 2928, 2822, 2323, 2203, 2117, 1746, 1648, 1572, 1505, 1430, 1356, 1281, 1237, 1196, 1152, 1027, 980.

CI-MS (m/z): 335 (M^++1), 306, 225, 151, 96, 90.

Preparation 23:

1-[4-(4-Azido-2,6-difluoro-phenyl)-piperzin-1-yl]-2-(*tert*-butyl-dimethyl-silanyloxy)-ethanone



The title compound was prepared from 4-[(4-azido-2-fluoro-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester and (450 mg, 75%) was obtained from (*tert*-Butyl-dimethyl-silanyloxy)-acetyl chloride[2] (308 mg, 1.46 mmol) following the same procedure as described for the preparation of [4-(4-azido-2,6-difluoro-phenyl)-piperazin-1-yl]-(5-nitro-furan-2-yl)-methanone (Preparation 19).

2.Wilssner, A.; Grudzinskas, C.V.; J. Org. Chem., 1978, 43, 3972

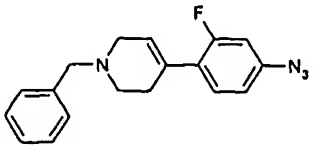
^{1}H NMR ($CDCl_3$): δ 6.45 (d, J = 9.3 Hz, 2H), 4.20 (s, 2H). 3.57 (bs, 4H), 3.02 (bs, 4H), 0.79 (s, 9H), 0.09 (s, 6H).

IR (KBr, cm^{-1}): 3405, 2930, 2856, 1667, 1524, 1470, 1256, 1119, 1045, 938, 859, 805, 779, 670, 605, 564.

CI-MS (m/z): 412 (M^++1), 383, 354, 326, 307, 231, 193, 144, 105, 91.

Preparation 24:

4-(4-Azido-2-fluoro-phenyl)-1-benzyl-1, 2, 3, 6-tetrahydro-pyridine:



The title compound was prepared from 4-(1-benzyl-1, 2, 3, 6-tetrahydro-pyridin-4-yl)-3-fluoro-phenylamine (6 grams, 21.2 mmol), obtained from preparation 12, by following the same procedure as described for 1-[4-(4-Azido-2-fluoro -phenyl)-piperazin-1-yl]-ethanone, in 38% yield. (Preparation 15).

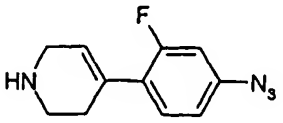
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.45-7.18 (m, 6H), 6.82-6.62 (m, 2H), 6.01-5.96 (m, 1H), 3.69 (s, 2H), 3.25-3.18 (m, 2H), 2.81-2.62 (m, 2H), 2.61-2.42 (m, 2H)

IR (Neat): 3029, 2923, 2113, 1609, 1498, 1308 cm^{-1}

CI-MS (m/e): 309 (M^++1)

Preparation 25:

4-(4-Azido-2-fluoro-phenyl)-1, 2, 3, 6-tetrahydro-pyridine



1-Chloromethylchloroformate (3.89 mL, 35.71mmol.) was added to an ice cold solution of 4-(4-Azido-2-fluoro-phenyl)-1-benzyl-1, 2, 3, 6-tetrahydro-pyridine (10 grams, 32.46 mmol), obtained in preparation 24, in dichloromethane (DCM) (70 mL).

This solution was allowed to stir at 0 °C for 1 hour. Solvent was evaporated under vacuum and the residue was refluxed in methanol for 2 hours. Then the solvent was removed under vacuum and the residue was purified by column chromatography (0.05:1 methanol: chloroform) to obtain desired product as yellow solid. (5 grams, 71%)

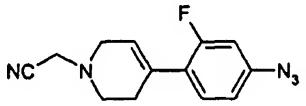
^{1}H NMR ($CDCl_3$, 200MHz): δ 7.30-7.05 (m, 1H), 6.80-6.62 (m, 2H), 6.00-5.86 (m 1H), 3.97-3.75 (m, 2H), 3.57-3.30 (m, 2H), 2.97-2.75 (m, 2H).

IR (KBr): 3425, 2926, 2116, 1498, 1309, 1206, 807, 600 cm^{-1}

CI-MS (m/e): 219 (M+1)

Preparation 26:

[4-{4-Azido-phenyl}-3, 6-dihydro-2H-pyridin-1-yl] – acetonitrile



To a solution of 4-(4-Azido-2-fluoro-phenyl)-1, 2, 3, 6-tetrahydro-pyridine (0.4 grams, 1.80 mmol), obtained in preparation 25, and potassium carbonate (0.79 grams, 5.5 mmol) in dry dimethyl formamide (DMF) (8 mL) was added bromoacetonitrile (2.2 grams, 18.30 mmol) at 0 °C . Allowed the reaction mixture to stir at 25-35 °C for 12 hours. The reaction mixture was then diluted with ethyl acetate (15 mL), washed with water followed by brine solution. The organic layer was evaporated under reduced pressure and the residue was purified by column chromatography (0.1:1 ethylacetate/pet.ether) to give the desired product as a yellow solid (0.09 grams, 36%)

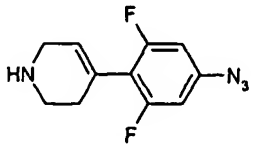
^{1}H-NMR ($CDCl_3$, 200MHz): δ 7.28-7.19 (m, 1H), 6.82-6.70 (m, 2H), 5.98-5.90 (m, 1H), 3.67 (s, 2H), 3.34-3.30 (m, 2H), 2.87 (t, J=5.4 Hz, 2H), 2.70-2.58 (m, 2H).

IR (Neat): 2924, 2113, 1616, 1500, 1208, 977, 860 cm^{-1}

CI-MS (m/e): 258 (M+1)

Preparation 27:

4-(4-Azido-2, 6-difluoro-phenyl)-1, 2, 3, 6-tetrahydro-pyridine



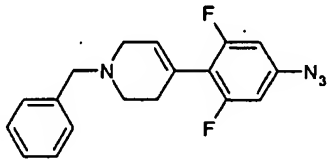
The title compound (6 grams, 68%) was obtained from 4-(1-benzyl-1, 2, 3, 6-tetrahydro-pyridin-4-yl)-3, 5-difluoro-phenylamine, obtained in preparation 13, using the same procedure as described for synthesis of 4-(4-azido-2-fluoro-phenyl)-1, 2, 3, 6-tetrahydro-pyridine (Preparation 25).

^{1}H NMR ($CDCl_3$, 200MHz): δ 6.60(d, J=7.7 Hz, 2H), 6.02-5.89(m, 1H), 3.40-3.28(m, 2H), 2.87(t, J= 5.5Hz, 2H), 2.60-2.48 (m, 2H).

IR (KBr): 3421, 2925, 2741, 2741, 2599, 2473, 2117, 1613, 1206, 1095, 1035 cm^{-1}

Preparation 28:

4-(1-Benzyl-1, 2, 3, 6-tetrahydro-pyridin-4-yl)-3,5-difluoro-phenylazide :



The title compound was prepared from 4-(1-Benzyl-1, 2, 3, 6-tetrahydro-pyridin-4-yl)-3, 5-difluoro-phenylamine (6 grams, 20 mmol), obtained from preparation 13, following the same procedure as described for the preparation of 1-[4-(4-azido-2-fluoro - phenyl)-piperazin-1-yl]-ethanone (Preparation 7), in 62% yield.

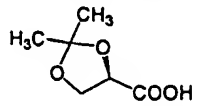
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.48-7.28 (m, 5H), 6.57 (d, J = 8.3 Hz, 2H), 5.89-5.72 (m, 1H), 3.67 (s, 2H), 3.22-3.18 (m, 2H), 2.72 (t, J = 5.6 Hz, 2H), 2.59-2.32 (m, 2H)

IR (KBr): 2920, 2801, 2115, 1632, 1570, 1492, 1436, 1436, 1342, 1235 cm^{-1}

CI-MS (m/e): 327 (M+1), 298

Preparation 29:

(*R*)-2,2-Dimethyl-1,3-dioxolane-4-carboxylic acid

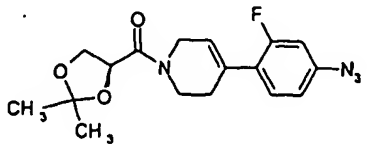


To a solution of methyl-(*R*)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (1.8 grams, 11.24 mmol) in THF (20 mL) was added an aqueous solution (20 mL) of lithium hydroxide monohydrate (0.71 grams, 16.9 mmol) drop wise over a period of 10 minutes at 0 °C and stirring was continued for another 1 hour. The reaction mixture was diluted with 50 mL of water and extracted with ethyl acetate (50 mL), which was discarded. Further, the aqueous layer was acidified with 10 M phosphorous acid (H_3PO_4) and the pH was brought to 2. The aqueous layer was then extracted with ethyl acetate (50 mL x 4) and the

combined organic layers were washed with water and brine and dried over sodium sulfate. Removal of volatiles left 1.6 grams (97%) of the title acid, which was used directly for the next step.

Preparation 30:

[4-(4-Azido-2-fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-((4S)-2,2-dimethyl-[1,3] dioxolan-4-yl)-methanone



To a solution of 2, 2-dimethyl-[1, 3] dioxolane-4-carboxylic acid, obtained in preparation 29, in dry THF (4 mL) was added isobutylchloroformate (103 mg, 0.757 mmol) and triethylamine (84 mg, 0.825 mmol) at 0 °C. The reaction mixture was stirred for 10 minutes, followed by the addition of 4-(4-Azido-2-fluoro-phenyl)-1, 2, 3, 6-tetrahydro-pyridine (150 mg, 0.688 mmol), obtained in preparation 25. The reaction mixture was allowed to stir for 16 hours at 25-35 °C after which it was diluted with ethyl acetate (5 mL), washed with saturated sodium bicarbonate solution and brine. The organic layer was distilled off under vacuum and the residue was purified by column chromatography to furnish the desired product as a viscous liquid. (150 mg, 63%)

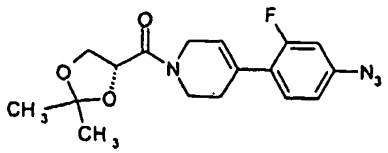
^{1}H NMR ($CDCl_3$, 200MHz): δ 7.30-7.15 (m, 1H), 6.88-6.68 (m, 2H), 6.01-5.90 (m, 1H), 4.80-4.66 (m, 1H), 4.58-4.40 (m, 1H), 4.40-4.24 (m, 1H), 4.24-4.05 (m, 2H), 4.04-3.82 (m, 2H), 3.82-3.56 (m, 1H), 2.76-2.36 (m, 2H), 1.43 (s, 6H);

IR (Neat): 2959, 2114, 1646, 150, 1210, 1070, 845, 767 cm^{-1}.

CI-MS (m/e): 347 (M+1);

Preparation 31:

[4-(4-Azido-2-fluoro-phenyl)-3,6-dihydro-2H--pyridin-1-yl]-((4R)-2,2-dimethyl-[1,3]dioxolan-4-yl)-methanone



The title compound (260 mg) was synthesized from 4-(4-Azido-2-fluoro-phenyl)-1, 2, 3, 6-tetrahydro-pyridine (300 mg, 1.376 mmol), obtained in preparation 25, by the same procedure as described for [4-(4-Azido-2-fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-((4S)-2,2-dimethyl-[1,3] dioxolan-4-yl)-methanone (Preparation 30).

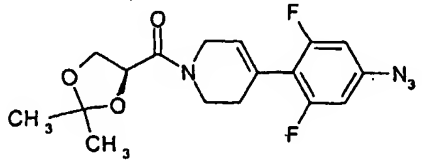
^{1}H NMR ($CDCl_3$, 200MHz): δ 7.30-7.15(m, 1H), 6.88-6.68(m, 2H), 6.01-5.90(m, 1H), 4.80-4.66(m, 1H), 4.55-4.40(m, 1H), 4.40-4.24(m, 1H), 4.24-4.05(m, 2H), 4.00-3.82(m, 1H), 3.80-3.58 (m, 1H), 2.66-2.40 (m, 2H), 1.42 (s, 6H).

IR (Neat): 2987, 1644, 1449, 1374, 1211, 1068, 847 cm^{-1}

CI-MS (m/e): 347 (M+1)

Preparation 32:

[4-(4-Azido-2, 6-difluoro-phenyl)-3, 6-dihydro-2H-pyridin-1-yl]-((4S)-2,2-dimethyl-[1, 3] dioxolan-4-yl)-methanone



The desired product (600 mg) was obtained from 4-(4-azido-2, 6-difluoro-phenyl)-1, 2, 3, 6-tetrahydro-pyridine (687 mg, 2.91 mmol), obtained in preparation 27, by the same procedure as described for the preparation of [4-(4-azido-2-fluoro-phenyl)-3,6-dihydro-2H--pyridin-1-yl]-(2,2-dimethyl-[1,3]dioxolan-4-yl)-methanone (Preparation 30).

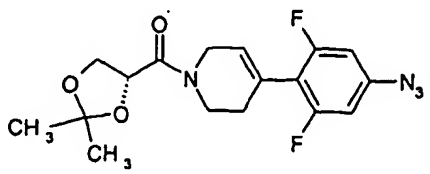
^{1}H NMR ($CDCl_3$, 200MHz): δ 6.62 (d, J=4.8Hz, 2H), 5.90-5.70 (m, 1H), 4.80-4.60 (m, 1H), 4.60-4.42 (m, 1H, 4.42-4.27 (m, 1H), 4.27-4.05 (m, 2H), 4.05-3.85 (m, 1H, 3.85-3.62 (m, 1H), 2.70-2.28 (m,2H), 1.43(s, 6H).

IR (Neat): 2988, 1633, 1438, 1343, 1057, 928, 732 cm^{-1}

CI-MS (m/e): 365 (M+1)

Preparation 33:

[4-(4-Azido-2, 6-difluoro-phenyl)-3, 6-dihydro-2H-pyridin-1-yl]-((4R)-2, 2-dimethyl-[1, 3] dioxolan-4-yl)-methanone



The title compound (770 mg) was obtained from 4-(4-azido-2, 6-difluoro-phenyl)-1, 2, 3, 6-tetrahydro-pyridine (500 mg, 3.42 mmol), obtained in preparation 27, and (S)-2,2-dimethyl-1,3-dioxalane-4-carboxylic acid, by the same procedure as described for the preparation of [4-(4-azido-2-fluoro-phenyl)-3,6-dihydro-2H--pyridin-1-yl]-(2,2-dimethyl-[1,3]dioxolan-4-yl)-methanone (Preparation 30).

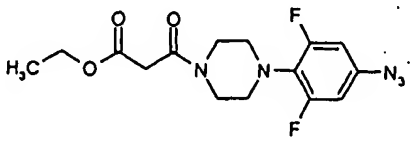
^{1}H NMR ($CDCl_3$, 200MHz): δ 6.59(d, J=7.8Hz, 2H), 5.90-5.70(m, 1H), 4.73(t, J=6.3Hz, 1H), 4.60-4.41(m, 1H), 4.41-4.25(m, 1H), 4.25-4.08(m, 2H), 4.08-3.85(m, 1H), 3.80-3.60(m, 1H), 2.72-2.30(m, 2H), 1.42(s, 6H).

IR(Neat): 2988, 2202, 2117, 1570. 1449, 1344, 1059, 981 cm^{-1}

CI-MS (m/e): 365 (M+1)

Preparation 34:

3-[4-(4-Azido-2,6-difluoro-phenyl)- piperazin-1-yl]-3-oxo-propionic acid ethyl ester



To a stirred solution of 1-(4-Azido-2,6-difluoro-phenyl)-piperazine, obtained in the process of preparation 19 (500 mg, 2.1 mmol) in dry dichloromethane (DCM) (15 mL) was added triethylamine (0.9 ml, 6.3 mmol) and ethylmalonyl chloride (0.53 mL, 4.18 mmol) and 4-Dimethylamino-pyridine (DMAP) catalytic amount at 0 °C . The reaction mixture was diluted with DCM and washed with water (2 x 15mL), brine, dried over sodium sulfate. (Na_2SO_4) The organic solvent was distilled off under vacuum and the residue was purified by column chromatography (4:6 ethyl acetate/pet.ether) to give the title compound (600 mg, 81%).

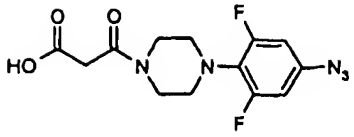
^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.56 (d, J = 9.7 Hz, 2H), 4.22 (q, J = 7.0 Hz, 2H), 3.76 (t, J = 4.8 Hz, 2H), 3.56 (t, J = 4.8 Hz, 2H), 3.50 (s, 2H), 3.18 – 3.11 (m, 4H), 1.30 (t, J = 7.3 Hz, 3H).

IR (KBr): 2923, 2116, 1739, 1652, 1504, 1443, 1237, 1154, 1028, 846 cm^{-1}.

CI-MS (m/e): 354 (M^++1), 328

Preparation 35:

3-[4-(4-Azido-2,6-difluoro-phenyl)- piperazin-1-yl]-3-oxo-propionic acid



To a stirred solution of 3-[4-(4-Azido-2,6-difluoro-phenyl)- piperazin-1-yl]-3-oxo-propionic acid ethyl ester (100 mg, 0.28 mmol) obtained in preparation 34, in THF:H_2O (4:1) solution was added lithium hydroxide (9 mg, 0.37 mmol) in minimum amount of water and stirred for 2 hours at 25-35 °C. The reaction mixture was acidified with ortho phosphoric acid till pH = 2 and the extracted with ethyl acetate and concentrated under vacuum to yield the corresponding free acid which was pure enough to carry next step (60 mg, 65%).

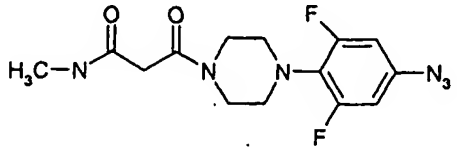
^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.69 (d, J = 9.4 Hz, 2H), 3.82 (t, J = 4.8 Hz, 2H), 3.60 (t, J = 4.8 Hz, 2H), 3.42 (s, 2H), 3.21 – 3.15 (m, 4H).

IR (neat): 2922, 2854, 2117, 1736, 1610, 1504, 1445, 1237, 1033, 756 cm^{-1}

CI-MS (m/e): 282, 256

Preparation 36:

3-[4-(4-Azido-2, 6-difluoro-phenyl)- piperazin-1-yl]-N-methyl-3-oxo-propionamide



To a stirred solution of 3-[4-(4-Azido-2,6-difluoro-phenyl)- piperazin-1-yl]-3-oxo-propionic acid (150 mg, 0.46 mmol) obtained in preparation 35, in dry DMF (8 mL) was added methylamine in THF (29 mg, 0.92 mmol), N –Methyl morpholine (47 mg, 0.46 mmol) and Benzotriazol-1-yloxytris (dimethyl-amino) phosphonium hexafluorophosptate (BOP) (204 mg, 0.46 mmol) portion wise at 0 °C. The reaction mixture was stirred for 9 to 13 hours at 25-35 °C. Then the reaction mixture was diluted with ethyl acetate (20 mL) and washed with water (2 x 10 mL), brine and dried (Na_2SO_4). The solvent was removed under vacuum and the residue was purified by column chromatography (1% $CH_3OH/CHCl_3$) to furnish the title compound (90 mg, 57%).

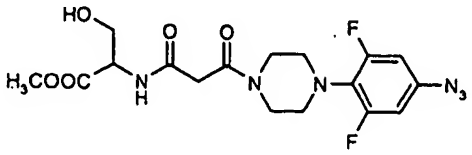
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44 (bs, 1H), 6.56 (d, J = 9.1 Hz, 2H), 3.75 (t, J = 4.8 Hz, 2H), 3.66 (t, J = 4.6 Hz, 2H), 3.36 (s, 2H), 3.18 -3.10 (m, 4H), 2.84 (d, J = 4.8 Hz, 3H).

IR (KBr): 3320, 2923, 2115, 1632, 1505, 1451, 1240, 1031, 834 cm^{-1}.

CI-MS (m/e): 339 (M^++1), 310

Preparation 37:

2(S)-{3-[4-(4-Azido-2,6-difluoro-phenyl)-piperazin-1-yl]-3-oxo-propionylmino}-3-hydroxy-propionic acid methyl ester



The title compound was prepared from was synthesized from 1-(4-Azido-2,6-difluoro-phenyl)-piperazine, obtained in the process of preparation 19, and 2-amino-3-hydroxy-propionic acid methyl ester using the same procedure as described for synthesis of 3-[4-(4-Azido-2, 6-difluoro-phenyl)- piperazin-1-yl]-N-methyl-3-oxo-propionamide (preparation 36).

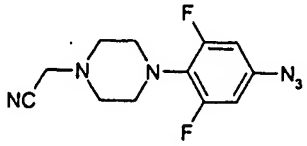
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01 (d, J = 6.4 Hz, 1H), 6.58 (d, J = 9.5 Hz, 2H), 4.70 – 4.65 (m, 1H), 4.05 – 3.96 (m, 2H), 3.80 (s, 3H), 3.78 (t, J = 5.0 Hz, 2H), 3.63 (t, J = 5.6 Hz, 2H), 3.44 (d, J = 2.5 Hz, 2H), 3.21- 3.11 (m, 4H).

IR (KBr): 3319, 2115, 1746, 1630, 1504, 1442, 1235, 1033, 754 cm^{-1}

CI-MS (m/e): 427 (M^++1), 409

Preparation 38:

[4-(4-Azido-2,6-difluoro-phenyl)-piperazin-1-yl]-acetonitrile



To a stirred solution of 1-(4-Azido-2,6 -difluoro-phenyl)-piperazine, obtained in the process of preparation 19, (1.5 grams, 6.27 mmol) in dry DMF (10 mL) was added anhydrous potassium carbonate (K_2CO_3) (5.2 grams, 37.6 mmol) and stirred at for 5 minutes. Then bromoacetonitrile was added drop wise at 25-35 °C.and stirred for 9 to 13 hours. The reaction mixture was diluted with ethylacetate and washed with water (2 x25 mL), brine and dried over Na_2SO_4. The organic layer was concentrated under vacuum and the purified by column chromatography (8:2 ethyl acetate (EtOAc)/pet ether) to give the title product (1 gram, 59 %)

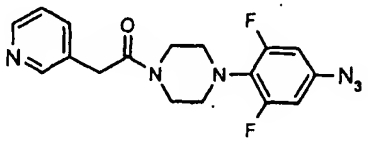
^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.55 (d, J = 9.7 Hz, 2H), 3.57 (s, 2H), 3.25 – 3.18 (m, 4H), 2.73-2.69 (m, 4H).

IR (Neat): 2831, 2116, 1503, 1235, 1009, 780 cm^{-1}

CI-MS (m/e): 279 (M^++1), 252, 226

Preparation 39:

1-[4-(4-Azido-2, 6-difluoro-phenyl) - piperazin-1-yl]-2-pyridin-3-yl-ethanone



The title compound (200 mg, 67%) was synthesized from pyridin-3-yl-acetic acid (145 mg, 0.84 mmol) using the same procedure as described in example 27.

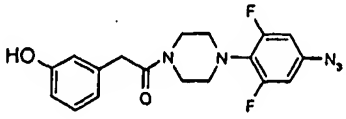
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.56 -8.51 (m, 2H), 7.66 (d, J = 7.8 Hz, 1H), 7.32 – 7.27 (m, 1H), 6.55 (d, J = 9.4 Hz, 2H), 3.78 – 3.75 (m, 2H), 3.76 (s, 2H), 3.59 (t, J = 4.8 Hz, 2H), 3.12 – 3.09 (m, 2H), 3.10 – 3.05 (m, 2H).

IR (KBr): 2115, 1645, 1574, 1504, 1441, 1238, 1152, 1029, 846, 712 cm^{-1}

CI-MS (m/e): 359 (M^++1), 330

Preparation 40:

1-[4-(4-Azido-2,6-difluoro-phenyl) - piperazin-1-yl]-2-(3-hydroxy-phenyl)-ethanone



The title compound (250 mg, 53 %) was synthesized from (3-Hydroxy-phenyl)-acetic acid (191 mg, 1.25 mmol) and 1-(4-Azido-2,6-difluoro-phenyl)-piperazine, obtained in the process of preparation 19, using the same procedure as described in example 27.

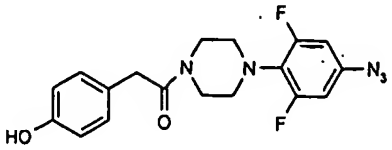
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.17 (t, J = 7.8 Hz, 1H), 6.86 (t, 2.1Hz, 1H), 6.78 – 6.73 (m, 2H), 6.53 (d, J = 9.7 Hz, 2H), 3.78 – 3.72 (m, 2H), 3.73 (s, 2H), 3.55 (t, J = 4.8 Hz, 2H), 3.09 (t, J = 4.8 Hz, 2H), 2.97 – 2.95 (m, 2H).

IR (KBr): 3277, 2113, 1640, 1509, 1442, 1240, 1030, 836, 679 cm^{-1}.

CI-MS (m/e): 373 (M^+)

Preparation 41:

1-[4-(4-Azido-2,6-difluoro-phenyl)- piperazin-1-yl]-2-(4-hydroxy-phenyl)-ethanone



The title compound (160 mg, 81%) was synthesized from (4-Hydroxy-phenyl)-acetic acid (80 mg, 0.53 mmol) and 1-(4-Azido-2,6-difluoro-phenyl)-piperazine, obtained in the process of preparation 19, applying the same procedure as described in example 27.

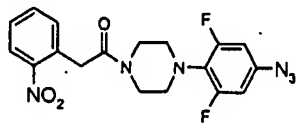
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.10 (d, J = 8.6 Hz, 2H), 6.79 -6.75 (d, J = 8.5 Hz, 2H), 6.56 – 6.51 (d, J = 9.6 Hz, 2H), 5.19 (s, 1H), 3.75 (t, J = 4.8 Hz, 2H), 3.69 (s, 2H), 3.55 (t, J = 4.8 Hz, 2H), 3.15 – 3.05 (m, 2H), 3.01 – 2.95 (m, 2H).

IR (KBr): 3246, 2116, 1631, 1509, 1443, 1237, 1029, 730 cm^{-1}.

CI-MS (m/e): 373 (M^+), 345

Preparation 42:

1-[4-(4-Azido-2,6-difluoro-phenyl)- piperazin-1-yl]-2-(2-nitro-phenyl)- ethanone



The title compound (470 mg, 56 %) was synthesized from (2-nitro-phenyl)-acetic acid (379 mg, 2.09 mmol) and 1-(4-Azido-2,6-difluoro-phenyl)-piperazine, obtainted in the process of preparation 19, using the same procedure as described in example 27.

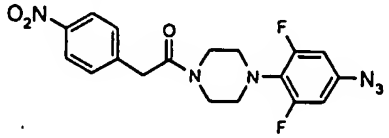
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.10 (d, J= 8.1 Hz, 1H), 7.63 -7.34 (m, 3H), 6.56(d, J = 9.7 Hz, 2H), 4.10 (s, 2H), 3.80-3.62 (m, 4H), 3.30-3.21(m, 2H), 3.20-3.06 (m, 2H).

IR (KBr): 2113, 1653, 1575, 1524, 1504, 1440, 1352, 1237, 1155, 1026, 728 cm^{-1}.

CI-MS (m/e): 403 (M^++1), 377

Preparation 43:

1-[4-(4-Azido-2,6-difluoro-phenyl)- piperazin-1-yl]-2-(4-nitro-phenyl)- ethanone



The title compound (490 mg, 58 %) was synthesized from (4-Nitro-phenyl)-acetic acid (379 mg, 2.09 mmol) and 1-(4-Azido-2,6-difluoro-phenyl)-piperazine, obtained in the process of preparation 19, using the same described in example 27.

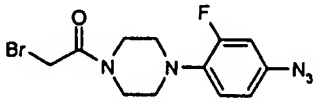
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.22-8.19(m, 2H), 7.44(d, J=8.9 Hz, 2H), 6.60-6.53(m, 2H), 3.85(s, 2H), 3.77(t, J = 5.1 Hz, 2H), 3.58(t, J= 4.8 Hz, 2H), 3.12(t, J= 4.6 Hz, 2H), 3.10-3.05(m, 2H).

IR (KBr): 2118, 1651, 1575, 1511, 1441, 1349, 1288, 1022, 739 cm^{-1}

CI-MS (m/e): 402 (M^+), 374, 346

Preparation 44:

1-[4-(4-Azido-2-fluoro-phenyl)-piperazin-1-yl]-2-bromo-ethanone



To a stirred solution of 1-(4-Azido-2-fluoro-phenyl)-piperazine, obtained in the process of preparation 20 (400 mg, 1.81 mmol) in dry DCM at 0 °C was added triethylamine (0.8 mL) followed by the drop wise addition of bromoacetyl bromide (0.3 mL) and catalytic amount of DMAP. The mixture was stirred 9 to 13 hours at 25-35 °C.

The solvent was removed under vacuum and the residue was purified by column chromatography (1:9 EtOAc/Pet. Ether) to afford desired product (140 mg, 23%).

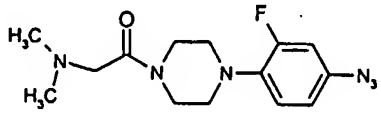
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.14 – 6.84 (m, 2H), 6.78 – 6.72(m 1H), 3.89 (s, 2H), 3.84 – 3.76 (m, 2H), 3.75 – 3.60 (m, 2H), 3.22 – 2.94 (m, 4H).

IR (KBr): 3438, 2853, 2114, 1655, 1509, 1435, 1294, 1224, 1162, 1032, 808, 753 cm^{-1}.

CI-MS (m/e): 344 (M^++2), 303

Preparation 45:

1-[4-(4-Azido-2-fluoro-phenyl)-piperazin-1-yl]-2-dimethylamino-ethanone



To a stirred mixture of N,N-dimethylamine (0.26 mL, 2M solution in methanol), potassium carbonate (170 mg, 1.23 mmol) and dry DMF (2 mL) was added 1-[4-(4-Azido-2-fluoro-phenyl)-piperazin-1-yl]-2-bromo-ethanone (140 mg, 0.40 mmol) obtained in preparation 44, in dry DMF (3 mL) drop wise at room te,perature and stirred for 9 to 13

hours. Then the reaction mixture was diluted with ethyl acetate (20 mL) and washed with water (2 x 15 mL), brine and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by column chromatography (3.5: 6.5 EtOAc/pet ether) to furnish the title compound (100 mg, 80 %).

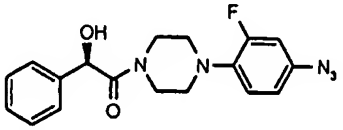
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.16-6.82 (m, 2H), 6.81-6.65 (m, 1H), 3.92-3.62 (m, 4H), 3.18 (s, 2H), 3.16-2.92 (m, 4H), 2.32 (s, 6H).

IR (Neat): 2825, 2114, 1648, 1506, 1460, 1232, 1147, 1029, 859, 755 cm^{-1}.

CI-MS (m/e): 307(M^++1), 281, 266.

Preparation 46:

1-[4-(4-Azido-2-difluoro-phenyl)- piperazin-1-yl]-2(R)-hydroxy-2-phenyl- ethanone



The title compound (87 mg, 11 %) was synthesized from hydroxyl phenyl-acetic acid (344 mg, 2.26 mmol) and 1-(4-Azido-2-fluoro-phenyl)-piperazine obtained in the process of preparation 20, applying the same procedure as described in example 27.

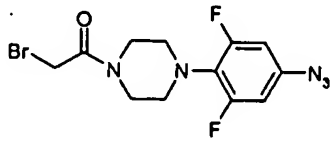
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.48 – 7.30 (m, 5H), 7.14 – 6.84 (m, 2H), 6.76 (t, J = 8.5 Hz, 1H), 5.24 (d, J = 5.3 Hz, 1H), 4.74 (bs, 1H), 4.12 – 3.82 (m, 1H), 3.80 – 3.62 (m, 1H), 3.56 – 3.22 (m, 2H), 3.20 – 2.66 (m, 4H).

IR (Neat): 3407, 2113, 1644, 1505, 1450, 1386, 1234, 1025, 763, 703 cm^{-1}.

CI-MS (m/e): 356 (M^++1), 328, 314, 299

Preparation 47:

1-[4-(4-Azido-2,6-difluoro-phenyl)- piperazin-1-yl]-2-bromo-ethanone



The title compound (1.12 grams, 37%) was synthesized from bromo acetyl bromide (1.5 mL, 16.7 mmol) and 1-(4-Azido-2,6-difluoro-phenyl)-piperazine, obtained in the process of preparation 19, using the the same procedure as described in preparation 44.

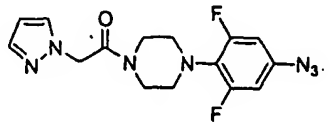
^{1}H NMR (200 MHz, $CDCl_3$): δ 6.57 (d, J = 9.5 Hz, 2H), 3.89 (s, 2H), 3.82 – 3.68 (m, 2H), 3.66 – 3.58 (m, 2H), 3.28 – 3.04 (m, 4H).

IR (KBr): 3423, 2114, 1745, 1635, 1504, 1446, 1236, 1028, 971, 846 cm^{-1}.

CI-MS (m/e): 362 (M^++2), 360

Preparation 48:

1-[4-(4-Azido-2,6-difluoro-phenyl)- piperazin-1-yl]-2-pyrazol-1-yl-ethanone



The title compound (160 mg, 47%) was synthesized from 1-[4-(4-Azido-2,6-difluoro-phenyl)- piperazin-1-yl]-2-bromo-ethanone (350 mg, 0.97 mmol) obtained in preparation 47, employing the same procedure as described in preparation 45.

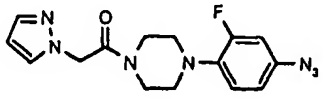
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.58 (s, 1H), 7.25 (s, 1H), 6.56 (d, J=9.3 Hz, 2H), 6.34 (s, 1H), 5.04(s, 2H), 3.78-3.58 (m, 4H), 3.18-2.98 (m, 4H).

IR (KBr): 3108, 2118, 1656, 1570, 1506, 1237, 1150, 1034, 819, 771 cm^{-1}

CI-MS (m/e): 348 (M^++1)

Preparation 49:

1-[4-(4-Azido-2-fluoro-phenyl)-piperazin-1-yl]-2-pyrazol-1-yl-ethanone



Using the same procedure as described in preparation 45, the title compound (162 mg, 53 %) was synthesized from 1-[4-(4-Azido-2-fluoro-phenyl) - piperazin-1-yl]-2-bromo-ethanone (322 mg, 0.94 mmol) obtained in preparation 44.

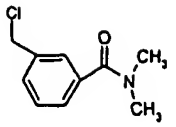
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.56 (s, 2H), 6.98 – 6.68 (m, 3H), 6.38 (s, 1H), 5.04 (s, 2H), 3.86 – 3.64 (m, 4H), 3.12 – 2.92 (m, 4H).

IR (KBr): 3102, 2117, 1663, 1509, 1308, 1239, 1212, 1156, 1095, 1026, 814, 772 cm-1.

CI-MS (m/e): 330 (M^++1), 304, 289

Preparation 50:

3-Chloromethyl-N,N-dimethyl-benzamide



To a stirred solution 3-chloromethyl benzoyl chloride (0.07ml, 0.53 mmol) in DCM at 0 °C was added dimethylamine (1.6 mL, 2M in methanol) drop wise and stirred for 9 to 13 hours at 25-35 °C. The solvent was removed under vacuum and the residue was purified by column chromatography (1.5:8.5 EtOAc/pet ether) to afford the title product (85 mg, 81 %).

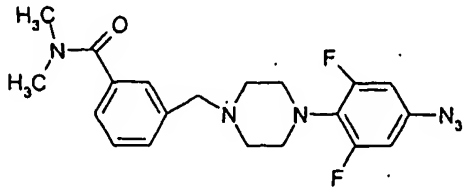
^{1}H NMR (200MHz, $CDCl_3$): δ 7.45-7.32 (m, 4H), 4.59 (s, 2H), 3.18 (s, 3H), 2.94 (s, 3H).

IR (Neat): 3419, 2926, 1743, 1633, 1393, 1264, 1173, 1078, 710 cm^{-1}.

CI-MS (m/e): 198 (M^++1), 153

Preparation 51:

3-[4-(4-Azido-2,6-difluoro-phenyl)- piperazin-1-ylmethyl]-N,N-dimethyl- benzamide



To a stirred solution of 1-(4-Azido-2,6-difluoro-phenyl)-piperazine, obtained in the process of preparation 19 (80 mg, 0.33 mmol) in dry DMF (3 mL) was added potassium carbonate (138 mg, 1 mmol) at 25-35 °C followed by the drop wise addition of 3-chloromethyl-N,N-dimethyl-benzamide (99 mg, 0.5 mmol) obtained in preparation 50, as a solution in DMF (3 mL). The reaction mixture was stirred at 25-35 °C 9 to 13 hours. The mixture was diluted with EtOAc (25 mL) and washed with water (2 x 20 mL) and brine. The organic layers were dried over sodium sulphate and concentrated under vacuum. The residue was purified by column chromatography (3:7 EtOAc/ Pet. ether) to afford title compound (85 mg, 63%).

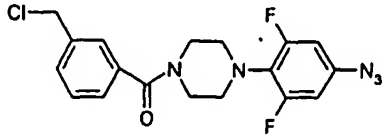
^{1}H NMR (400MHz, $CDCl_3$): δ 8.09 – 7.98 (m, 2H), 7.48 – 7.24 (m, 2H), 6.56 (d, J = 9.2 Hz, 2H), 3.59 (s, 2H), 3.22 – 3.09 (m, 2H), 3.03 – 2.94 (m, 2H), 2.86 (s, 6H), 2.64 – 2.50 (m, 4H).

IR (Neat): 2817, 2113, 1636, 1502, 1449, 1391, 1238, 1027, 927, 772 cm^{-1}.

CI-MS (m/e): 401 (M^++1), 372

Preparation 52:

[4-(4-Azido-2,6-difluoro-phenyl)-piperazin-1-yl]-(3-chloromethyl-phenyl)-methanone



The title compound (700 mg, 29 %) was synthesized from 3-Chloromethyl-benzoyl chloride (1.78 mL, 12.6 mmol) and 1-(4-Azido-2,6-difluoro-phenyl)-piperazine, obtained in the process of preparation 19, using the same procedure as described in preparation 34.

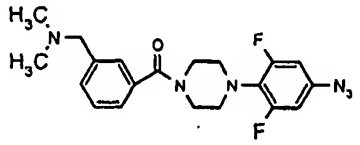
^{1}H NMR (200MHz, $CDCl_3$): δ 7.78-7.28 (m, 4H), 6.58 (d, J=9.5 Hz, 2H), 5.02 (s, 2H), 4.26-3.78 (m, 2H), 3.64-3.48 (m, 2H), 3.42-3.24 (m, 2H), 3.24-2.98 (m, 2H).

IR (KBr): 3420, 2115, 1634, 1503, 1388, 1238, 1207, 1024, 829, 710 cm^{-1}.

CI-MS (m/e): 392 (M^++1)

Preparation 53:

[4-(4-Azido-2,6-difluoro-phenyl)-piperazin-1-yl]- (3-dimethylaminomethyl-phenyl)-methanone



To a stirred solution of [4-(4-Azido-2,6-difluoro-phenyl)-piperazin-1-yl]-(3-chloromethyl-phenyl)-methanone (700 mg, 1.78 mmol) obtained in preparation 52, in DCM was added N,N-dimethylamine (5.4 mL) drop wise at 0 °C and stirred for 9 to 13 hours at 25-35 °C. The solvent was removed under vacuum and the residue was purified by column chromatography (7:3 EtOAc/pet.ether) to afford the title product (250 mg, 35 %).

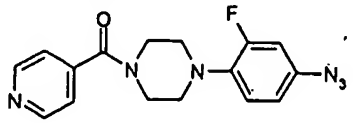
^{1}H NMR (200MHz, $CDCl_3$): δ 7.42-7.22 (m, 4H), 6.58 (d, J=8.9 Hz, 2H), 3.88-3.72 (m, 2H), 3.70-3.36 (m, 2H), 3.50(s, 2H), 3.38-3.02 (m, 4H), 2.38(s, 6H).

IR (KBr): 2114, 1636, 1574, 1503, 1239, 1027, 844, 744 cm^{-1}.

CI-MS (m/e): 401 (M^++1)

Preparation 54:

[4-(4-Azido-2-fluoro-phenyl)-piperazin-1-yl]-pyridin-4-yl-methanone



The title compound (143 mg, 49 %) was synthesized from Isonicotinic acid (112 mg, 0.91 mmol) and 1-(4-Azido-2-fluoro-phenyl)-piperazine obtained in the process of preparation 20, applying the same procedure as described in example 27.

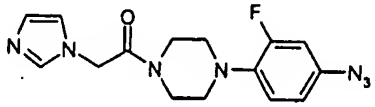
^{1}H NMR (200MHz, $CDCl_3$): δ 8.82 – 8.86 (m, 2H), 7.35 (d, J = 4.8 Hz, 2H), 7.14 – 6.78 (m, 3H), 4.08 – 3.84 (m, 2H), 3.64 – 3.42 (m, 2H), 3.30 – 2.88 (m, 4H).

IR (KBr): 2114, 1641, 1505, 1437, 1286, 1233, 1159, 1018, 922, 834, 756, 638 cm^{-1}.

CI-MS (m/e): 327 (M^++1), 286

Preparation 55:

1-[4-(4-Azido-2-fluoro-phenyl)- piperazin-1-yl]-2-imidazol-1-yl-ethanone



The title compound (72 mg, 47%) was synthesized from 1-[4-(4-azido-2-fluoro-phenyl)-piperazin-1-yl]-2-bromo-ethanone (161 mg, 0.47 mmol) obtained in preparation 44, and imidazole following same procedure as described in preparation 45.

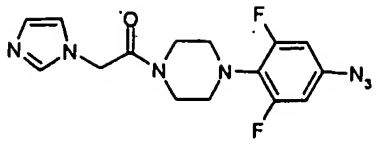
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.59 (s, 1H), 7.19 – 6.72 (m, 5H), 4.86 (s, 2H), 3.94 – 3.78 (m, 2H), 3.76 – 3.58 (m, 2H), 3.19 – 2.96 (m, 4H),

IR (Neat): 2115, 1661, 1507, 1428, 1232, 1033, 810, 755, 662 cm^{-1}

CI-MS (m/e): 330 (M^++1), 304, 289

Preparation 56:

1-[4-(4-Azido-2,6 -fluoro-phenyl)- piperazin-1-yl]-2-imidazol-1-yl-ethanone



The title compound (400 mg, 55%) was synthesized from 1-[4-(4-Azido-2,6-fluoro-phenyl)-piperazin-1-yl]-2-bromo-ethanone (750 mg, 2.08 mmol) obtained in preparation 47, and imidazole using the same procedure employed in preparation 45.

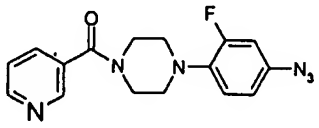
^{1}H NMR (200MHz, $CDCl_3$): δ 7.62 (s, 1H), 7.15 (s, 1H), 7.07 (s, 1H), 6.57 (d, J = 9.5 Hz, 2H), 4.82 (s, 2H), 3.84 -3.66 (m, 2H), 3.64 – 3.44 (m, 2H), 3.22 – 3.04 (m, 4H).

IR (KBr): 2124, 1666, 1505, 1440, 1242, 1036, 834, 662 cm^{-1}.

CI-MS (m/e): 348 (M^++1), 322

Preparation 57:

[4-(4-Azido-2-fluoro-phenyl)-piperazin-1-yl]-Pyridin-3-yl-methanone



The title compound (178 mg, 60 %) was synthesized from nicotinic acid (111 mg, 0.91 mmol) and 1-(4-Azido-2-fluoro-phenyl)-piperazine, obtained in the process of preparation 20, following the same procedure as described in example 27.

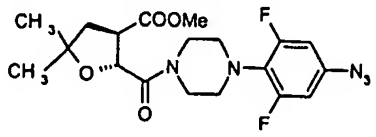
^{1}H NMR (200MHz, $CDCl_3$): δ 8.80 – 8.59 (m, 2H), 7.88 – 7.72 (m, 1H), 7.49 – 7.29 (m, 1H), 7.18 – 6.84 (m, 2H), 6.80 – 6.64 (m, 1H), 4.18 – 3.44 (m, 4H), 3.36 – 2.64 (m, 4H).

IR (KBr): 2114, 1637, 1505, 1436, 1285, 1236, 1159, 1012, 814, 755 cm^{-1}.

CI-MS (m/e): 327 (M^++1), 301, 286

Preparation 58:

5(R)-[4-(4-Azido-2, 6-difluoro-phenyl)-piperazine-1-carbonyl]-2,2-dimethyl - [1, 3] dioxolane-4(R) -carboxylic acid methyl ester



The title compound (10 grams, 47 %) was synthesized from 2,2-Dimethyl-[1,3]dioxolane-4 (R),5 (R) -dicarboxylic acid monomethyl ester (12 grams, 41.8 mmol)

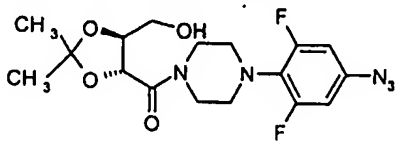
and 1-(4-Azido-2,6-difluoro-phenyl)-piperazine, obtained in the process of preparation 19, using the procedure as described in example 27.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.56 (d, J = 9.6 Hz, 2H), 5.35 (d, J = 6.0 Hz, 1H), 4.93 (d, J = 4.0 Hz, 1H), 4.81 (s, 3H), 4.36 – 4.18 (m, 4H), 3.24 – 3.12 (m, 4H).

CI-MS (m/e): 411(M^+-15), 397(M^+-28).

Preparation 59:

[4-(4-Azido-2,6-difluoro-phenyl)-piperazin-1-yl]-(5(S)-hydroxymethyl-2,2-dimethyl-[1, 3] dioxolan-4(R)-yl)-methanone



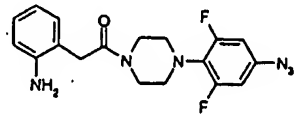
To a stirred solution of 5-[4-(4-Azido-2,6-difluoro-phenyl)-piperazine-1-carbonyl]-2,2-dimethyl-[1,3]dioxolane-4-carboxylic acid methyl ester (2 grams, 4.7 mmol) obtained in preparation 58, in methanol at 0 °C was added sodium borohydride (356 mg, 9.4 mmol) portion wise and stirred at 25-35 °C for 3 – 4 hours. The methanol was removed under vacuum and the residue was purified by column chromatography (0.3:1 EtOAc/pet ether) to give title compound (1 gram, 55%).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.57 (d, J = 9.6 Hz, 2H), 4.76 – 4.64 (m, 1H), 4.54 (d, J = 7.2 Hz, 1H), 3.99 – 3.54 (m, 6H), 3.38 – 2.96 (m, 4H), 1.46 (s, 3H), 1.41 (s, 3H).

CI-MS (m/e): 398 (M^+ + 1), 372

Preparation 60:

2-(2-Amino-phenyl)-1-[4-(4-azido-2, 6-fluoro-phenyl)-piperazin-1-yl]-ethanone



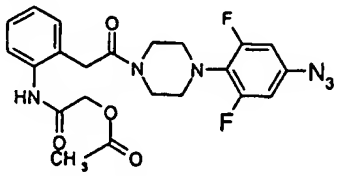
The title compound (60 mg, 63%) was synthesized from 1-[4-(4-azido-2,6-difluoro-phenyl)- piperazin-1-yl]-2-(2-nitro-phenyl)- ethanone (100 mg, 0.25 mmol) obtained in preparation 42, using the same procedure as described in example 95.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.16-6.92 (m, 2H), 6.80 – 6.62 (m, 2H), 6.54 (d, J=9.5 Hz, 2 H), 3.80 – 3.58 (m, 6 H), 3.18 – 2.91 (m, 4 H).

CI-MS (m/e): 373 (M^+ + 1)

Preparation 61:

Acetic acid (2-{2-[4-(4-azido-2,6-fluoro-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-phenylcarbamoyl)-methyl ester



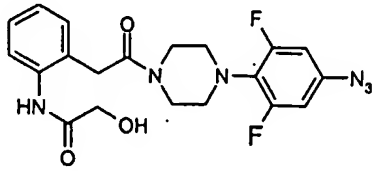
To a stirred solution of 2-(2-Amino-phenyl)-1-[4-(4-azido-2, 6-fluoro-phenyl)-piperazin-1-yl]-ethanone (60 mg, 0.16 mmol) obtained in preparation 60, was added triethylamine (0.06 mL) and acetoxy acetylchloride (0.03 mL) and catalytic amount of DMAP at 0 °C. The reaction mixture was diluted with DCM and washed with water (2 x 10 mL), brine and then dried over sodium sulphate. The solvent was removed under vacuum and the residue was purified by column chromatography (2.5: 7.5 EtOAc/Pet.Ether) to yield title product (50 mg, 65%).

^{1}H NMR ($CDCl_3$,400 MHz): δ 10.48 (bs, 1H), 7.99 (d, J = 8.1 Hz, 1H), 7.36-7.29(m, 1H), 7.16 – 7.08 (m, 2H), 6.56 (d, J=9.3 Hz, 2H), 4.77 (s, 2H), 3.81 (t, J=4.7 Hz, 2H), 3.72 (s, 2 H), 3.72 – 3.64 (m, 2 H), 3.21-3.04 (m, 4H), 2.16 (s, 3H).

CI-MS (m/e): 473 (M^+ + 1), 447

Preparation 62:

N-(2-{2-[4-(4-Azido-2,6-difluoro-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-phenyl)-2-hydroxy-acetamide



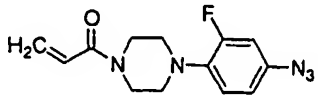
To a stirred solution of acetic acid (2-{2-[4-(4-azido-2,6-fluoro-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-phenylcarbamoyl)-methyl ester (50 mg, 0.11 mmol) obtained in preparation 61, in methanol at 0 °C was added aqueous ammonia (2 to 3 drops) and stirred for 3 – 4 hours. The methanol was removed under vacuum and the residue was purified by column chromatography (0.6:1 EtOAc/pet ether) to give the title product (25 mg, 54%).

^{1}H NMR ($CDCl_3$,400 MHz): δ 10.13 (bs, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.38-7.30 (m, 1H), 7.19-7.09 (m, 2H), 6.55(d, J= 9.6 Hz, 2H), 4.30 (s, 2H), 3.76 (s, 2H), 3.74-3.65(m, 4H), 3.12-3.08 (m, 4H).

CI-MS (m/e): 431 (M^+ + 1), 405

Preparation 63:

1-[4-(4-Azido-2-fluoro-phenyl)-piperazin-1-yl]-propenone



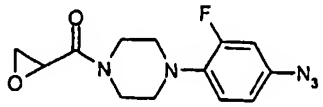
The title compound (630 mg, 50 %) was synthesized from acryloyl chloride (1.25 grams, 13.8 mmol) and 1-(4-Azido-2-fluoro-phenyl)-piperazine, obtained in the process of preparation 20, following the same procedure as described in preparation 34.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.18 – 6.82 (m, 2H), 6.80 – 6.44 (m, 2H), 6.31 (dd, J_1 = 1.9 Hz, J_2 = 16.8 Hz, 1H), 5.73 (dd, J_1 = 1.9 Hz, J_2 = 10.3 Hz, 1H), 3.98 – 3.54 (m, 4H), 3.22 – 2.84 (m, 4H).

CI-MS (m/e): 276 (M^+ + 1), 250, 235

Preparation 64:

[4-(4-Azido-2-fluoro-phenyl)-piperazin-1-yl]-oxiranyl-methanone



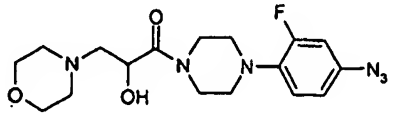
n-Butyl lithium (0.41 mL, 1.6 M in hexane) was added to a solution of tert-butyl hydroperoxide (TBHP). (0.2 mL, 4M in toluene) in THF (5 mL) at -78 °C . The mixture was stirred for 5 minutes. A solution of (1-[4-(4-Azido-2-fluoro-phenyl)-piperazin-1-yl]-propenone (150 mg, 0.54 mmol) obtained in preparation 63, in dry THF (5 mL) was added to the reaction mixture and stirred for 9 to 13 hours. Sodium sulfite (21.6 mg, 0.1 mmol) was added and stirred for 20 minutes. The reaction mixture was diluted with DCM (30 mL) and filtered through celite bed. The filtrate was concentrated under vacuum and the residue was purified by column chromatography (0.6: 1 EtOAc: Pet Ether) to yield the title compound (30 mg, 18 %).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.28 – 6.82 (m, 3H), 3.99 – 3.72 (m, 4H), 3.66 (t, J = 3.3 Hz, 1H), 3.24 – 3.06 (m, 4H), 3.01 (d, J = 3.0 Hz, 2H).

CI-MS (m/e): 292 (M^+ + 1), 251

Preparation 65:

1-[4-(4-Azido-2-fluoro-phenyl)-piperazin-1-yl]-2-hydroxy-3-morpholin-4-yl-propan-1-one



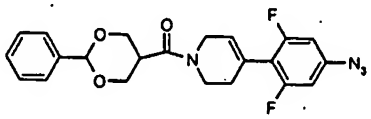
[4-(4-Azido-2-fluoro-phenyl)-piperazin-1-yl]-Oxiranyl-methanone (85 mg, 0.292 mmol) obtained in preparation 64, and morpholine (9 mg, 0.1mmol) were refluxed in isopropanol (10 mL) for 1 hour . The reaction mixture was further heated at 50 °C for 2 hours. Then it was allowed to come to 25-35 °C for 9 to 13 hours. The solvent was removed under vacuum and the residue was purified by column chromatography (0.7: 1 EtOAc: Pet Ether) to obtain the desired product (80 mg, 72 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.97 – 6.89 (m, 2H), 6.80 – 6.72 (m, 1H), 4.60 – 4.48 (m, 1H), 3.94 – 3.86 (m, 1H), 3.82 – 3.62 (m, 8H), 3.16 – 3.02 (m, 4H), 2.78 – 2.54 (m, 6H).

CI-MS (m/e): 379 (M^+ + 1), 353, 338

Preparation 66:

[4-(4-Azido-2,6-difluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-(2-phenyl-[1,3]dioxan-5-yl)-methanone



The title compound (100 mg, 50 %) was synthesized from 2-Phenyl-[1,3]dioxane-5-carboxylic acid (92 mg, 0.47 mmol) (Ref: *J.Org.Chem.*, 62, 4029 – 4035, 1997) and 4-(4-azido-2,6-difluorophenyl)-1,2,3,6-tetrahydro-pyridine employing the procedure as described in example 27.

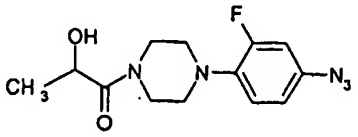
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.58 – 7.44 (m, 2H), 7.44 – 7.31 (m, 3H), 6.60 (d, J = 8.4 Hz, 2H) 5.94 – 5.80 (m, 1H), 5.57 (s, 1H), 4.48 – 4.11 (m, 6H), 3.81 (t, J = 5.3 Hz, 2H), 3.55 – 3.31 (m, 1H), 2.60 – 2.36 (m, 2H).

IR (KBr): 3423, 2113, 1626, 1569, 1437, 1388, 1237, 1150, 1093, 1028, 753 cm^{-1}.

CI-MS (m/e): 398 (M^+-28), 292.

Preparation 67:

1-[4-(4-Azido-2-fluoro-phenyl)-piperazin-1-yl]-2-hydroxy-propan-1-one



The title compound (90 mg, 13 %) was synthesized from 2-hydroxy-propionic acid (200 mg, 2.26 mmol) and 1-(4-Azido-2-fluoro-phenyl)-piperazine, obtained in the process of preparation 20, following the same procedure as described in example 27.

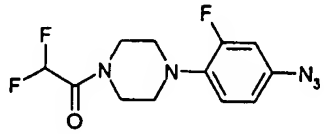
1H NMR (CDCl3, 200 MHz): δ 7.15 – 6.98 (m, 1H), 6.97 – 6.82 (m, 1H), 6.81 – 6.66 (m, 1H), 4.57 – 4.38 (m, 1H), 4.01 – 3.66 (m, 3H), 3.64 – 3.46 (m, 2H), 3.18 – 2.92 (m, 4H), 1.36 (d, J = 6.5 Hz, 3H).

IR (Neat): 3423, 2924, 2115, 1644, 1507, 1443, 1230, 1129, 1037, 936, 876, 726 cm^{-1}.

ES-MS (m/e): 294 (M^++1)

Preparation 68:

1-[4-(4-Azido-2-fluoro-phenyl)-piperazin-1-yl]-2,2-difluoro-ethanone



The title compound (110 mg, 28 %) was synthesized from difluoro acetic acid (130 mg, 1.35 mmol) and 1-(4-Azido-2-fluoro-phenyl)-piperazine, obtained in the process of preparation 20, using the same procedure as described in example 27.

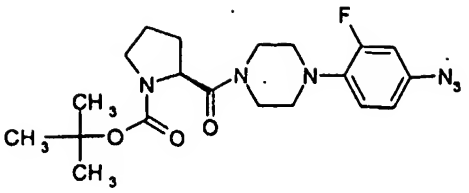
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.16 – 6.99 (m, 1H), 6.92 (t, J = 8.7 Hz, 1H), 6.76 (d, J = 10.9 Hz, 1H), 6.13 (t, J = 53.6 Hz, 1H), 3.90 – 3.66 (m, 4H), 3.10 – 2.97 (m, 4H).

IR (KBr): 3449, 2829, 2116, 1674, 1507, 1235, 1137, 1031, 844, 725, 564 cm^{-1}.

CI-MS (m/e): 300 (M^++1), 274, 259

Preparation 69:

2(S)-[4-(4-Azido-2-fluoro-phenyl)-piperazine-1-carbonyl]-pyrrolidine-1-carboxylic acid tert-butyl ester



The title compound (1.3 grams, 69 %) was synthesized from pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (1 gram, 4.65 mmol) and 1-(4-Azido-2-fluoro-phenyl)-piperazine, obtained in the process of preparation 20, following the same procedure as described in example 27.

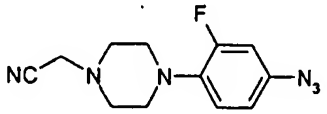
1H NMR (CDCl3, 200 MHz): δ 7.16 – 6.82 (m, 2H), 6.81 – 6.67 (m, 1H), 4.80 – 4.50 (m, 1H), 3.94 – 3.30 (m, 6H), 3.26 – 2.90 (m, 4H), 2.20 – 1.98 (m, 2H), 1.96 – 1.76 (m, 2H), 1.46 (s, 9H).

IR (Neat): 3481, 2976, 2113, 1695, 1659, 1506, 1450, 1400, 1229, 1162, 1126, 1033, 755, 663 cm^{-1}.

CI-MS (m/e): 419 (M^++1), 393, 378, 337, 322, 293

Preparation 70:

[4-(4-Azido-2-fluoro-phenyl)-piperazin-1-yl]-acetonitrile



The title compound (395 mg, 46 %) was synthesized from 1-(4-Azido-2, fluoro-phenyl)-piperazine, obtained in the process of preparation 20, (720 mg, 3.26 mmol) applying the procedure as described in preparation 38.

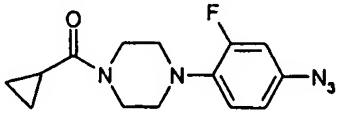
^1H NMR (400 MHz, $CDCl_3$): δ 7.10 – 7.00 (m, 1H), 7.00 – 6.90 (m, 1H), 6.80 – 6.76 (m, 1H), 3.56 (s, 2H), 3.18 – 3.09 (m, 4H), 2.82 – 2.75 (m, 4H).

IR (Neat): 3419, 2941, 2830, 2114, 1575, 1507, 1454, 1384, 1230, 1148, 1012, 912, 861, 812, 601 cm^{-1}.

CI-MS (m/e): 260 (M^+), 232

Preparation 71:

[4-(4-Azido-2-fluoro-phenyl)-piperazin-1-yl]-cyclopropyl-methanone



To a stirred solution of cyclopropyl carboxylic acid (134 mg, 1.58 mmol) and was added isobutylchloroformate (0.2 mL, 1.55 mmol) in dry DCM at 0 °C To this solution was added drop wise stirred solution of 1-(4-Azido-2, fluoro-phenyl)-piperazine (345 mg, 1.56 mmol) and triethylamine (0.32 mL, 3.10 mmol) in dry DCM and stirred at 25-35 °C for 9 to 13 hours. The reaction mixture was diluted with DCM and washed with water (2 x15 mL), brine and dried over Na_2SO_4. The organic layer was concentrated under vacuum and the residue was purified by column chromatography (4:6 EtOAc/pet ether) to give the title product (235 mg, 52%).

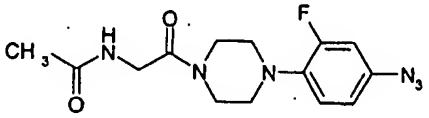
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 – 6.90 (m, 2H), 6.82 – 6.73 (m, 1H), 3.92 – 3.75 (m, 4H), 3.15 – 2.95 (m, 4H), 1.79 – 1.75 (m, 1H), 1.05 – 1.00 (m, 2H), 0.82 – 0.75 (m, 2H).

IR (KBr): 2922, 2112, 1640, 1505, 1438, 1229, 1035, 906, 804, 758 cm^{-1}.

CI-MS (m/e): 290 (M^++1), 249

Preparation 72:

N-{2-[4-(4-Azido-2-fluoro-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-acetamide



The title compound (40 mg, 15 %) was synthesized from N-acetyl glycine (105 mg, 0.89 mmol) and 1-(4-Azido-2-fluoro-phenyl)-piperazine, obtained in the process of preparation 20, using the same procedure as described in example 27.

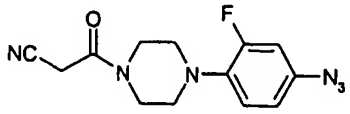
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.08 – 6.80 (m, 2H), 6.80 – 6.74 (m, 1H), 6.73 – 6.39 (m, 1H), 4.10 (d, J = 3.9 Hz, 2H), 3.90 – 3.78 (m, 2H), 3.65 – 3.58 (m, 2H), 3.15 – 2.95 (m, 4H), 2.06 (s, 3H).

IR (Neat): 3336, 2924, 2115, 1642, 1505, 1442, 1384, 1232, 1033, 773 cm^{-1}.

CI-MS (m/e): 321 (M^++1), 295, 280

Preparation 73:

3-[4-(4-Azido-2-fluoro-phenyl)-piperazin-1-yl]-3-oxo-propionitrile



The title compound (95 mg, 37%) was synthesized from cyano acetic acid (92 mg, 1.08 mmol) and 1-(4-Azido-2-fluoro-phenyl)-piperazine, obtained in the process of preparation 20, using the same procedure as described in example 27.

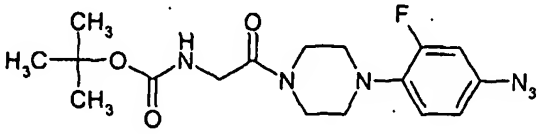
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.11 – 6.70 (m, 3H), 3.90 – 3.75 (m, 2H), 3.70 – 3.60 (m, 2H), 3.52 (s, 2H), 3.20 – 3.02 (m, 4H).

IR (Neat): 3424, 2923, 2358, 2114, 1653, 1586, 1506, 1039, 897, 761 cm^{-1}.

CI-MS (m/e): 289 (M^++1), 263, 248.

Preparation 74:

{2-[4-(4-Azido-2-fluoro-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-carbamic acid tert-butyl ester



The title compound (315 mg, 62%) was synthesized from N-Boc glycine (286 mg, 1.63 mmol) and 1-(4-Azido-2-fluoro-phenyl)-piperazine, obtained in the process of preparation 20, using the same procedure as described in example 27.

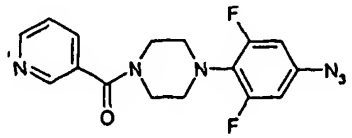
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.07 – 6.83 (m, 2H), 6.80 – 6.70 (m, 1H), 5.55 – 5.45 (m, 1H), 4.00 (d, J = 4.2 Hz, 2H), 3.99 – 3.79 (m, 2H), 3.79 – 3.55 (m, 2H), 3.15 – 2.98 (m, 4H), 1.45 (s, 9H).

IR (Neat): 3418, 2978, 2114, 1712, 1659, 1508, 1464, 1367, 1231, 1164 cm^{-1}.

CI-MS (m/e): 379 (M^++1), 353

Preparation 75:

[4-(4-Azido-2,6-difluoro-phenyl)-piperazin-1-yl]-Pyridin-3-yl-methanone



The title compound (130mg, 18 %) was synthesized from nicotinic acid (500 mg, 2.09 mmol) and 1-(4-Azido-2,6-difluoro-phenyl)-piperazine,obtained in the process of preparation19, using the procedure as described in example 27.

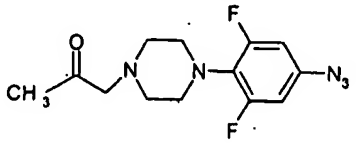
^{1}H NMR (200 MHz, $CDCl_3$): δ 8.70 – 8.67 (m, 2H), 7.79 (d, J = 7.3 Hz, 1H), 7.41 – 7.37 (m, 1H), 6.57 (d, J = 9.5 Hz, 2H), 4.00 – 3.80 (m, 2H), 3.70 – 3.50 (m, 2H), 3.30 – 3.00 (m, 4H).

IR (Neat): 3415, 2923, 2116, 1682, 1503, 1206, 1031, 836, 725 cm^{-1}.

CI-MS (m/e): 345 (M^++1), 319, 304

Preparation 76:

1-[4-(4-Azido-2,6-difluoro-phenyl)-piperazin-1-yl]-propan-2-one



The title compound (410mg, 54 %) was synthesized from chloroacetone (0.4 mL, 5.13 mmol) and 1-(4-azido-2,6-difluoro-phenyl)-piperazine, obtained in the process of preparation 19, following the same procedure as described as described in preparation 38.

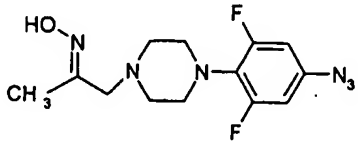
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.54 (d, J = 9.7 Hz, 2H), 3.23 – 3.19 (m, 6H), 2.61 – 2.59 (m, 4H), 2.18 (s, 3H).

IR (Neat): 3383, 2820, 2114, 1717, 1575, 1503, 1356, 1238, 1139, 1026, 928, 842 cm^{-1}.

CI-MS (m/e): 296 (M^++1), 268

Preparation 77:

1-[4-(4-Azido-2,6-difluoro-phenyl)-piperazin-1-yl]-propan-2-one oxime



To a stirred solution of 1-[4-(4-Azido-2,6-difluoro-phenyl)-piperazin-1-yl]-propan-2-one (70 mg, 0.24) obtained in preparation 76, in methanol was added drop wise solution of hydroxylamine hydrochloride (33 mg, 0.47 mmol) and sodium bicarbonate (40 mg, 0.47 mmol) in water and stirred at 25-35 °C for 9 to 13 hours. The reaction mixture was diluted with DCM and washed with water, brine and dried over Na_2SO_4. The organic layer was concentrated under vacuum and the residue was purified by column

chromatography (5.5:4.5 ethyl acetate/petroleum ether) to furnish the desired compound (45 mg, 59 %).

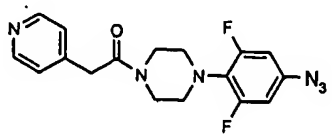
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.54 (d, J = 8.3 Hz, 2H), 3.20 – 3.17 (m, 4H), 3.06 (s, 2H), 2.59 – 2.52 (m, 4H), 1.95 (s, 3H).

IR (KBr): 3436, 2836, 2121, 1629, 1572, 1508, 1444, 1257, 1109, 942, 837, 609 cm^{-1}.

CI-MS (m/e): 311 (M^++1), 293, 263

Preparation 78:

1-[4-(4-Azido-2, 6-difluoro-phenyl) - piperazin-1-yl]-2-pyridin-4-yl-ethanone



The title compound (350 mg, 58 %) was synthesized from 4-pyridyl acetic acid (348 mg, 2 mmol) and 1-(4-Azido-2,6-difluoro-phenyl)-piperazine, obtained in the process of preparation 19, using the same procedure as described in example 27.

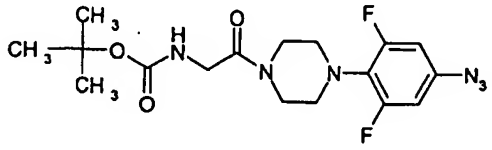
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 – 8.55 (m, 2H), 7.22 (d, J = 5.4 Hz, 2H), 6.56 (d, J = 8.2 Hz, 2H), 3.80 – 3.73 (m, 2H), 3.75 (s, 2H), 3.54 (t, J = 4.9 Hz, 2H), 3.11 (t, J = 4.8 Hz, 2H), 3.02 (t, J = 4.5 Hz, 2H)

IR (Neat): 3382, 2920, 2114, 1646, 1503, 1441, 1236, 1031, 965, 843, 769 cm^{-1}.

CI-MS (m/e): 359 (M^++1), 333

Preparation 79:

{2-[4-(4-Azido-2, 6-difluoro-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-carbamic acid tert-butyl ester



The title compound (2.2 grams, 48 %) was synthesized from N-Boc glycine (2.6 grams, 14.9 mmol) and 1-(4-azido-2,6-difluoro-phenyl)-piperazine, obtained in the process of preparation 19, using the same procedure as described in example 27.

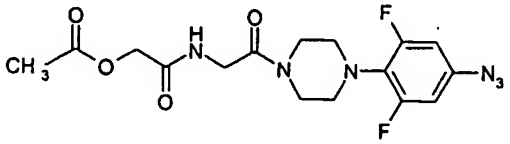
^{1}H NMR (200 MHz, $CDCl_3$): δ 6.57 (d, J = 9.5 Hz, 2H), 5.55 – 5.45 (m, 1H), 3.99 (d, J = 4.2 Hz, 2H), 3.74 (t, J = 4.9 Hz, 2H), 3.55 – 3.45 (m, 2H), 3.20 – 3.10 (m, 4H), 1.45 (s, 9H).

IR (KBr): 3306, 2973, 2114, 1710, 1653, 1502, 1554, 1447, 1366, 1279, 1165, 1028, 967, 840 cm^{-1}.

CI-MS (m/e): 398 (M^++2), 369, 341, 297

Preparation 80:

Acetic acid {2-[4-(4-azido-2,6-difluoro-phenyl)-piperazin-1-yl]-2-oxo-ethylcarbamoyl}-methyl ester



{2-[4-(4-Azido-2, 6-difluoro-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-carbamic acid tert-butyl ester (1 grams, 2.5 mmol) obtained in preparation 79, was treated with 60% TFA in DCM and stirred at 25-35 °C for 30 minutes and the reaction mixture was co-evaporated with toluene (2 x 20 mL) and extracted with ethyl acetate and concentrated to give 2-amino-1-[4-(4-azido-2,6-difluoro-phenyl)-piperazin-1-yl]-ethanone ,which was pure enough to be taken for further step directly To a stirred solution of 2-amino-1-[4-(4-azido-2,6-difluoro-phenyl)-piperazin-1-yl]-ethanone (730 mg, 2.5 mmoL) in dry DCM at 0 °C was added triethyl amine (1.0 mL, 7.4 mmol), acetoxy acetyl chloride (0.8 mL, 7.4 mmol) drop wise and stirred at 25-35 °C for 9 to 13 hours. The reaction mixture was diluted with DCM and washed with water, brine and dried over Na_2SO_4. The organic layer was concentrated under vacuum and the residue was purified by column chromatography (4:6 ethyl acetate/petroleum ether) to give the title product (670 mg, 68%).

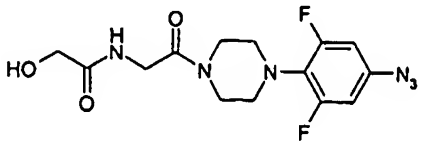
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40 – 7.30 (m, 1H), 6.57 (d, J = 9.5 Hz, 2H), 4.62 (s, 2H), 4.15 (d, J = 3.9 Hz, 2H), 3.76 (t, J = 4.8 Hz, 2H), 3.54 (t, J = 4.8 Hz, 2H), 3.20 – 3.05 (m, 4H), 2.17 (s, 3H).

IR (Neat): 3392, 2924, 2855, 2207, 2116, 1753, 1653, 1572, 1504, 1441, 1373, 1235, 1162, 1031, 843, 700 cm^{-1}.

CI-MS (m/e): 397 (M^++1), 368

Preparation 81:

N-{2-[4-(4-Azido-2,6-difluoro-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-2-hydroxy-acetamide



To a stirred solution of acetic acid {2-[4-(4-azido-2,6-difluoro-phenyl)-piperazin-1-yl]-2-oxo-ethylcarbamoyl}-methyl ester (210 mg, 0.53mmol) obtained in preparation 80, in methanol at 0 °C was added aqueous ammonia drop wise (5 to 6 drops) and stirred at 25-35 °C for 1hour. The solvent was removed and the residue was purified by column chromatography (7.5:2:5 ethyl acetate/ pet ether) to give the title product (175 mg, 93%)

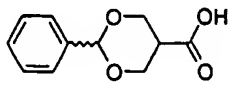
^{1}H NMR (400 MHz, DMSO): δ 7,71 (t, J=4.8 Hz, 1H), 6.94 (d, J=9.9 Hz, 2H), 5.68-5.60 (m, 2H), 4.09 (d, J=5.1 Hz, 2H), 3.85 (s, 2H), 3.60-3.48 (m, 4H), 3.10-3.00 (m, 4H).

IR (Neat): 3382, 2924, 2854, 2116, 1645, 1573, 1504, 1441, 1238, 1076, 1030, 579 cm^{-1}.

CI-MS (m/e): 355 (M^++1), 326, 240

Preparation 82:

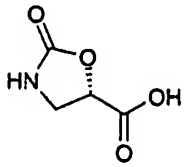
2-Phenyl-[1,3]dioxane-5-carboxylic acid



This compound was synthesized according to the procedure reported in *J. Org. Chem.* 1997, *62*, 4029-4035.

Preparation 83:

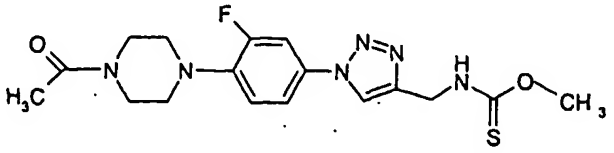
(*S*)-2-Oxo-oxazolidine-5-carboxylic acid



This compound was synthesized from (*S*)-malic acid following the procedure reported in *Synlett.* 2002, 2101-2103.

Example 1:

{1-[4-(4-Acetyl-piperazin-1-yl)-3-fluoro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl}-thiocarbamic acid *O*-methyl ester



To an ice cooled solution of 1-[4-(4-azido-2-fluoro-phenyl)-piperazin-1-yl]-ethanone (300 mg, 1.14 mmol) in DMF (5 mL), obtained in preparation 15, were added prop-2-ynyl-thiocarbamic acid *O*-methyl ester (176 mg, 1.37 mmol), diisopropylethylamine (198 µL, 1.14 mmol) and cuprous iodide (238 mg, 1.14 mmol) successively at 0 °C. The reaction mixture was stirred at 25-35 °C for 1 hour and then quenched with saturated ammonium chloride solution followed by 2-3 drops of ammonia and extracted with 5% methanol in chloroform (100 mL). The organic layer was washed successively with water and brine and then dried over sodium sulfate. The solvent was evaporated to afford the title compound (180 mg, 40%).

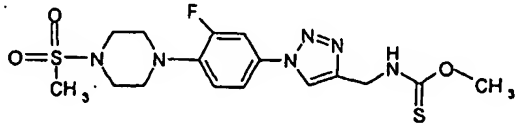
^{1}H NMR (DMSO-d_6): δ 9.65 (bs, 1H), 8.64 (d, J = 7.8 Hz, 1H), 7.84-7.67 (m, 2H), 7.21 (t, J = 8.9 Hz, 1H), 4.71 & 4.44 (2d, rotamers in a ratio of 4:1, J = 5.5 Hz, 2H), 3.95 & 3.88 (2s, rotamers in a ratio of 1:4, 3H), 3.61 (bs, 4H), 3.18-3.03 (m, 4H).

IR (KBr, cm^{-1}): 3428, 2926, 1636, 1520, 1440, 1226, 1059, 615.

CI-MS (m/z): 393(M^++1), 361, 319, 274, 257, 229, 181, 162, 130, 114.

Example 2:

{1-[3-Fluoro-4-(4-methanesulfonyl-piperazin-1-yl)-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl}-thiocarbamic acid *O*-methyl ester:



Title compound (415 mg, 58%) was prepared from 3-fluoro-4-(4-methanesulfonyl-piperazin-1-yl)-phenylazide (500 mg, 1.67 mmol), obtained in preparation 16, following the same procedure as descibed in the prepration of {1-[4-(4-acetyl-piperazin-1-yl)-3-fluoro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl}-thiocarbamic acid *O*-methyl ester (Example 1)

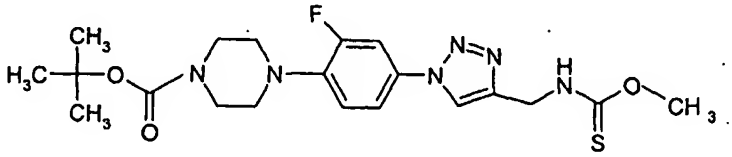
^{1}H NMR ($CDCl_3$): δ 8.07 (s, 1H), 7.56-7.42 (m, 2H), 7.06 (t, J = 8.8 Hz, 1H), 4.93 & 4.67 (2d, rotamers in a ratio of 4:1, J = 5.4 Hz, 2H), 4.13 & 4.01 (2s, rotamers in a ratio of 1:4, 3H), 3.47-3.43 (m, 4H), 3.29-3.26 (m, 4H), 2.87 (s, 3H).

IR (KBr, cm^{-1}): 3415, 2925, 2854, 1658, 1519, 1324, 1152, 1060, 969, 786, 518.

CI-MS (m/z): 429 (M^++1), 397, 381, 355, 310, 289, 259, 229.

Example 3:

4-{2-Fluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1, 2, 3] triazol-1-yl]-phenyl}-piperazine-1-carboxylic acid *tert*-butyl ester



Title compound (388 mg, 46%) was obtained from 4-(4-azido-2-fluoro-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (600 mg, 1.87 mmol), obtained in preparation 17, prop-2-ynyl-thiocarbamic acid *O*-methyl ester (288 mg, 2.24 mmol), obtained in preparation 1, diisopropylethyl amine (326 µL, 1.87 mmol) and cuprous iodide (356 mg, 1.87 mmol) following the same procedure descibed for the prepration of {1-[4-(4-acetyl-piperazin-1-yl)-3-fluoro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester (Example 1).

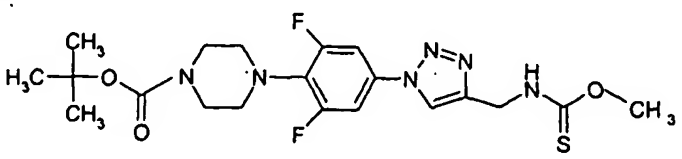
^{1}H NMR ($CDCl_3$): δ 8.04 & 7.81 (2s, rotamers in 4:1 ratio, 1H), 7.52-7.39 (m, 2H), 7.02-6.95 (m, 2H), 4.91 & 4.39 (2d, rotamers in 4:1 ratio, J = 5.9 Hz, 2H), 4.11 & 3.99 (2s, rotamers in 1:4 ratio, 3H), 3.62 (t, J = 4.6 Hz, 4H), 3.10 (t, J = 4.6 Hz. 4H), 1.49 (s, 9H).

IR (KBr, cm^{-1}): 3300, 3134, 2976, 2926, 2856, 1689, 1519, 1422, 1245, 1165, 1124, 1042, 994, 875, 826.

CI-MS (m/z): 451 (M^++1), 419, 363, 276, 232, 194,

Example 4:

4-{2,6-Difluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazine-1-carboxylic acid *tert*-butyl ester



Title compound (880 mg, 32%) was prepared from 4-(4-azido-2,6-difluoro-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (2.0 grams, 2.9 mmol), obtained in preparation 18 and following the same procedure as described for the preparation of {1-[4-(4-acetyl-piperazin-1-yl)-3-fluoro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester (Example 1).

Melting Point: 158-160 °C

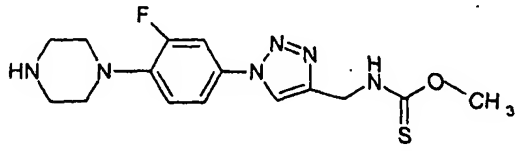
^{1}H NMR ($CDCl_3$): δ 8.04 & 7.81 (2s, rotamers in 4:1 ratio, 1H), 7.31-7.26 (m, 2H), 6.91 (bs, 1H), 4.90 & 4.65 (2d, rotamers in 4:1 ratio, J = 5.8 Hz, 2H), 4.11 & 3.99 (2s, rotamers in 1:4 ratio, 3H), 3.55 (bs, 4H), 3.18 (bs, 4H), 1.48 (s, 9H).

IR (KBr, cm^{-1}): 3199, 2925, 1688, 1518, 1170, 864, 555.

CI-MS (m/z): 469 (M^++1), 437, 413, 381, 294, 250, 163, 91.

Example 5:

[1-(3-Fluoro-4-piperazin-1-yl-phenyl)-1*H*-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid *O*-methyl ester



To an ice cold solution of 4-{2-fluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1, 2, 3]triazol-1-yl]-phenyl}-piperazine-1-carboxylic acid *tert*-butyl ester (550 mg, 1.22 mmol), obtained in Example 3, in DCM (1 mL) was added trifluoroacetic acid (2 mL) and stirred for 3 hours. The reaction mixture was then brought to pH = 8 by the addition of aqueous sodium bicarbonate and extracted with ethyl acetate (50 mL x 3). Combined ethyl acetate portion was washed with water followed by brine and dried over sodium sulfate. Evaporation of volatiles and purification of the residue by column chromatography (silica gel 60-120, 15:85 methanol/chloroform) yielded the title compound (260 mg, 61%).

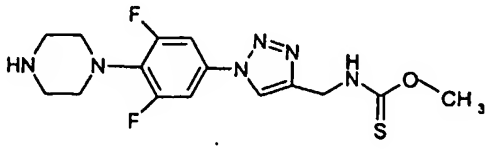
^{1}H NMR ($CDCl_3$): δ 8.73 (bs, 1H), 7.92 & 7.90 (2s, rotamers in 4:1 ratio, 1H), 7.27-7.12 (m, 2H), 6.73 (m, 1H), 4.46 & 4.19 (2s, rotamers in 4:1 ratio, 2H), 3.66 & 3.58 (2s, rotamers in 1:4 ratio, 3H), 3.06 (m, 8H).

IR (KBr, cm^{-1}): 3415, 2256, 1643, 1026, 1000, 827, 766, 538.

CI-MS (m/z): 351 (M^++1), 319, 303, 262, 232, 165, 147, 93.

Example 6:

[1-(3,5-Difluoro-4-piperazin-1-yl-phenyl)-1*H*-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid *O*-methyl ester



The title compound was prepared from 4-{2,6-difluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazine-1-carboxylic acid *tert*-butyl ester, obtained in example 4, and following the same procedure as described for the preparation of [1-(3-fluoro-4-piperazin-1-yl-phenyl)-1*H*-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid *O*-methyl ester (Example 5).

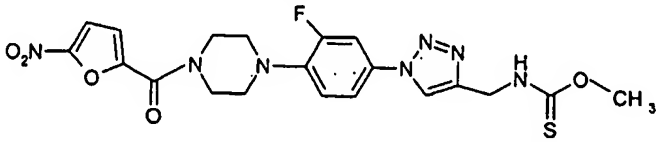
^{1}H NMR ($CDCl_3$) : δ 8.04 & 7.81 (2s, rotamers in ratio of 4:1, 1H), 7.33-7.22 (m, 2H), 7.07 (bs, 1H), 4.90 & 4.60 (2s, rotamers in ratio of 4:1, 2H), 4.11 & 3.99 (2s, rotamers in ratio of 1:4, 3H), 3.23-3.03 (m, 4H), 3.01-2.99 (m, 4H).

IR (KBr, cm^{-1}): 2837, 1516, 1401, 1201, 1137.

CI-MS: 369 (M^++1), 337, 295, 250.

Example 7;

(1-{3-Fluoro-4-[4-(5-nitro-furan-2-carbonyl)-piperazin-1-yl]-phenyl}-1*H* [1,2,3] triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester:



The title compound (150 mg, 28%) was obtained from [4-(4-azido-2-fluoro-phenyl)-piperazin-1-yl]-(5-nitro-furan-2-yl)-methanone (400 mg, 1.11 mmol), obtained in preparation 20, followed by the same procedure as described in the preparation of {1-[4-(4-acetyl-piperazin-1-yl)-3-fluoro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester (Example 1).

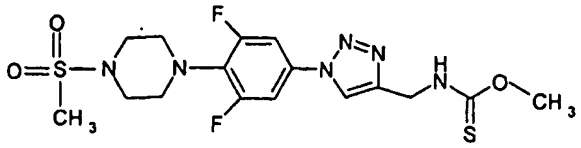
^{1}H NMR ($CDCl_3$): δ 8.06 (s, 1H), 7.55 (s, 1H), 7.49-7.38 (dd, J = 5.5 & 9.4 Hz, 2H), 4.90 (d, J = 5.9 Hz, 2H), 4.11-3.99 (m, 7H), 3.99 (bs, 4H).

IR (KBr, cm^{-1}): 3252, 2924, 1638, 1520.

CI-MS (m/z): 490 (M^++1), 458, 426, 393, 292.

Example 8:

{1-[3,5-Difluoro-4-(4-methanesulfonyl-piperazin-1-yl)-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl}-thiocarbamic acid *O*-methyl ester:



To an ice cold solution of 4-{2,6-difluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazine-1-carboxylic acid *tert*-butyl ester (200 mg, 0.43 mmol), obtained in example 4, in DCM (5 mL) was added 10 N HCl (0.43 mL, 4.27 mmol) and stirred for 15 minutes. An aqueous solution of sodium bicarbonate (717 mg) was then added to the reaction mixture. Resulting biphasic system was treated with methanesufonyl chloride (0.04 mL, 0.51 mmol) and stirred for 1 hour. Organic phase was separated, washed with water and brine successively and dried over sodium sulfate. Evaporation of the volatiles and purification of the resulting residue (silica gel 60-120, 1:1 acetone/chloroform) yielded the title compound (135 mg, 71%).

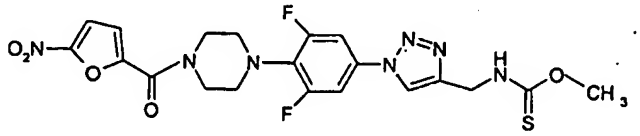
^{1}H NMR($CDCl_3$): δ 8.06 &7.80 (2s, 1H, rotamers in 4:1 ratio), 7.32 (d, J = 9.3 Hz, 2H), 6.89-6.91 (m, 1H), 4.91 & 4.66 (2d, J = 5.9 Hz, 2H, rotamers in 4:1 ratio), 4.12 & 4.00 (2s, rotamers in 1:4 ratio, 3H), 3.36 (s, 8H), 2.85 (s, 3H).

IR (KBr, cm^{-1}): 3336, 3141, 2920, 2855, 2361, 1747, 1520, 1451, 1408, 1322, 1268, 1207, 1144, 1024, 958, 840, 783, 666, 517.

CI-MS (m/z): 447 (M+1), 415, 328.

Example 9:

(1-{3,5-Difluoro-4-[4-(5-nitro-furan-2-carbonyl)-piperazin-1-yl]-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester:



The title compound (60 mg, 64%) was obtained from [4-(4-azido-2,6-difluoro phenyl)-piperazin-1-yl]-(5-nitro-furan-2-yl)-methanone, obtained in preparation 19, following the same procedure as described for the preparation of {1-[4-(4-acetyl-piperazin-1-yl)-3-fluoro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl}-thiocarbamic acid *O*-methyl ester (Example 1).

^{1}H NMR ($CDCl_3$): δ 8.06 & 7.80 (2s, rotamers in 4:1 ratio, 1H), 7.52 (d, J = 12.4 Hz, 1H), 7.44 (d, J = 9.4 Hz, 1H), 7.37 (d, J = 3.8 Hz, 1H), 7.24 (d, J = 5.4 Hz, 1H), 7.05 (t, J = 8.9

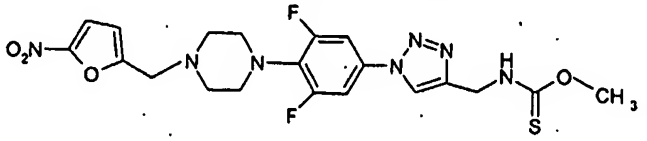
Hz, 1H), 6.90 (bs, 1H), 4.91 & 4.68 (2d, rotamers in 4:1 ratio, J = 5.9 Hz), 4.11-3.99 (m, 7H), 3.26 (bs, 4H).

IR (KBr,cm^{-1}): 3252, 2924, 1740, 1638, 1582, 1521, 1436, 1384, 1351, 1243, 1149, 1022, 971, 873, 812, 749.

CI-MS (m/z): 490, 458, 426, 393, 319, 292, 278, 251, 163, 116, 100.

Example 10:

(1-{3,5-Difluoro-4-[4-(5-nitro-furan-2-ylmethyl)-piperazin-1-yl]-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester:



Title compound (135 mg, 25%) was prepared from 1-(4-azido-2,6-difluoro-phenyl)-4-(5-nitro-furan-2-ylmethyl)-pipearazine (500 mg, 1.32 mmol), obtained in preparation 21, following the same procedure as described for the preparation of {1-[4-(4-acetyl-piperazin-1-yl)-3-fluoro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl}-thiocarbamic acid *O*-methyl ester (Example 1).

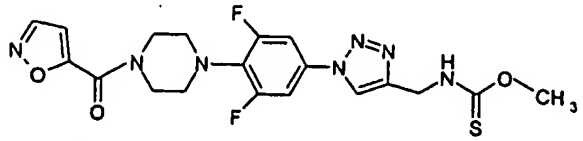
^{1}H NMR ($CDCl_3$): δ 8.01 & 7.71 (2s, rotamers in 4:1 ratio, 1H), 7.26 (d, J = 6.4 Hz, 2H), 6.85 (bs, 1H), 6.52 (d, J = 3.4 Hz, 1H), 4.88 & 4.62 (2d, rotamers in 4:1 ratio, J = 6.35 Hz, 2H), 4.09 & 3.97 (2s, rotamers in 1:4 ratio, 3H), 3.71 (s, 2H), 3.28 (bs, 4H), 2.67 (bs, 4H).

IR (KBr, cm^{-1}): 3404, 2930, 1590, 1518, 1454, 1393, 1355, 1233, 1143, 1023, 858, 811, 613.

CI-MS (m/z): 494 (M^++1), 462, 369, 337, 165, 158, 121.

Example 11:

(1-{3,5-Difluoro-4-[4-(isoxazole-5-carbonyl)-piperazin-1-yl]-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester:



The title compound (400 mg, 66.4%) was prepared from [4-(4-azido-2,6-difluoro-phenyl)-pipearazin-1-yl]-isoxazol-5-yl-methanone, obtained in preparation 22, following the same procedure as described for the preparation of {1-[4-(4-acetyl-piperazin-1-yl)-3-

fluoro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl}-thiocarbamic acid *O*-methyl ester (Example 1).

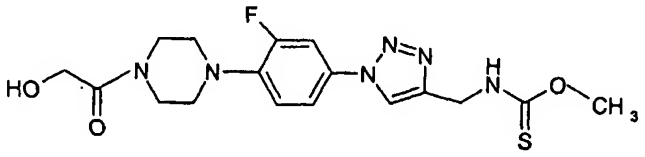
^{1}H NMR (CDCl3): δ 8.35 (d, J = 1.5 Hz, 1H), 8.07 & 7.83 (2s, rotamers in 4:1 ratio, 1H), 7.34 (d, J = 8.8 Hz, 2H), 6.94 (bs, 1H), 6.85 (s, 1H), 4.92 & 4.67 (2d, rotamers in 4:1 ratio, J = 5.9 Hz, 2H), 4.12 & 4.01 (2s, 3H, rotamers in 1:4 ratio), 3.91 (bs, 4H), 3.34 (bs, 4H).

IR (KBr, cm^{-1}): 3441, 2924, 1645, 1520, 1456, 1261, 1201, 1148, 1033, 981, 862, 755.

CI-MS (m/z): 464 (M^++1), 432, 369, 337, 309, 295, 250, 214, 196, 174, 149, 133, 92.

Example 12:

(1-{3-Fluoro-4-[4-(2-hydroxy-acetyl)-piperazin-1-yl]-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester:



To an ice cooled solution of 4-{2-fluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1, 2, 3] triazol-1-yl]-phenyl}-piperazine-1-carboxylic acid *tert*-butyl ester (235 mg, 0.5 mmol), obtained in example 3, was added trifluoroacetic acid (2 mL) and stirred at the same temperature for 1 hour. Excess of trifluoroacetic acid was removed on rotavapor and the resulting salt was washed with petroleum ether and dried under vacuum. To a solution of the salt in dichloromethane (10 mL) was added triethylamine (0.14 mL, 1 mmol) at 0 °C followed by the addition of *tert*-butyl dimethylsilyloxy acetyl chloride (120 mg, 0.5 mmol). The reaction mixture was then allowed to stir 9 to 13 hours at 25-35 °C.

Water was added to the reaction mixture and extracted with ethyl acetate (30 mL x 2). The combined organic portion was washed with water followed by brine and dried over sodium sulfate. The solvent was concentrated and the residue was dissolved in tetrahydro furan (5 mL) and tetrabutyl ammonium fluoride (160 mg, 0.5 mmol) was added to it. Stirring was continued for 2 hours. The reaction mixture was diluted with ethyl acetate and washed with water and brine successively. Organic layer was dried over sodium sulfate and volatiles were evaporated. The residue formed was passed through a silica gel column (60-120 mesh, eluent: ethyl acetate) to get 50 mg (25%) of the title compound.

^{1}H NMR ($CDCl_3$): δ 8.11 & 7.95 (2s, rotamers in 4:1 ratio, 1H), 7.51 (d, J = 12.7 Hz, 1H), 7.43 (d, J = 9.3 Hz, 1H), 7.02 (t, J = 8.8 Hz, 1H), 4.87 & 4.60 (2d, rotamers in 4:1 ratio, J

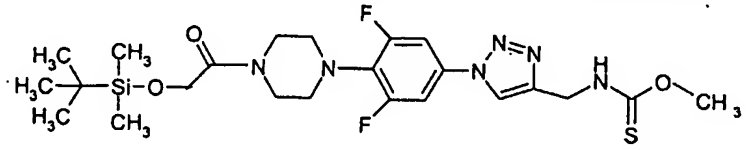
= 5.9 Hz, 2H), 4.22 (d, J = 3.9 Hz, 2H), 4.11 & 3.98 (2s, rotamers in 1:4 ratio, 3H), 3.85 (bs, 2H), 3.72 (bs, 1H), 3.50 (bs, 2H), 3.17 (bs, 4H)

IR (KBr, cm^{-1}): 3307, 3146, 2923, 2853, 1654, 1522, 1437, 1237, 1027, 982, 936, 867, 572.

CI-MS (m/z): 409 (M^++1), 377, 345, 320, 290, 190, 163, 146, 117, 103, 91.

Example 13:

[1-(4-{4-[2-(*tert*-Butyl-dimethyl-silanyloxy)-acetyl]-piperazin-1-yl}-3,5-difuoro-phenyl)-1*H*-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid *O*-methyl ester



Title compound (200 mg, 38%) was obtained from 1-[4-(4-azido-2,6-difluoro-phenyl)-piperzin-1-yl]-2-(*tert*-butyl-dimethyl-silanyloxy)-ethanone (400 mg, 0.97 mmol), obtained in preparation 23, following the same procdure as described for the preparation of {1-[4-(4-acetyl-piperazin-1-yl)-3-fluoro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl}-thiocarbamic acid *O*-methyl ester (Example 1).

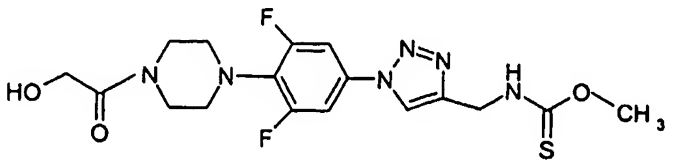
^{1}H NMR ($CDCl_3$): δ 8.02 & 7.76 (2s, rotamers in 4:1 ratio, 1H), 7.27 (d, J = 9.3 Hz, 2H), 6.85 (bs, 1H), 4.87 & 4.62 (2d, rotamers in 4:1 ratio, J = 5.9 Hz, 2H), 4.30 (s, 2H), 4.08 & 3.96 (2s, rotamers in 1:4 ratio, 3H), 3.69 (bs, 4H), 3.20 (bs, 4H), 0.89 (s, 9H), 0.09 (s, 6H).

IR (KBr, cm^{-1}): 3426, 3237, 2932, 2857, 1644, 1522, 1464, 1362, 1228, 1203, 1131, 1024, 842, 780, 581.

CI-MS (m/z): 541 (M^++1), 509, 483, 451, 423, 406, 364, 179, 93.

Example 14:

(1-{3,5-Difluoro-4-[4-(2-hydroxy-acetyl)-piperazin-1-yl]-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester:



Title compound (125 mg, 79%) was prepared from [1-(4-{4-[2-(*tert*-butyl-dimethyl-silanyloxy)-acetyl]-piperazin-1-yl}3,5-difuoro-phenyl)-1*H*-[1,2,3]triazol-4-ylmethyl]thiocarbamic acid *O*-methyl ester (200 mg, 0.77 mmol), obtained in example 13, upon treating with tetra-butyl ammonium fluoride (140 mg, 0.45 mmol) in THF (5 mL) at 25-35 °C for 2 hours. Extraction with ethylaceate and removal of volatiles under vacuum left a residue, which was passed through silica gel column (60% ethyl acetate: pet. ether) to give the title compound.

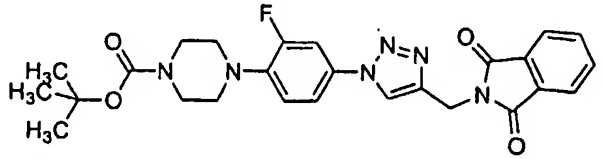
^{1}H NMR ($CDCl_3$): δ 8.08 & 7.85 (2s, rotamers in 1:4 ratio, 1H), 7.33 (d, J = 9.3 Hz, 2H), 7.05 (bs, 1H), 4.92 & 4.65 (2d, rotamers in 4:1 ratio, J = 5.9 Hz, 2H), 4.22 (d, J = 4.4 Hz, 2H), 4.11 & 3.99 (2s, rotamers in 1:4 ratio, 3H), 3.82 (bs, 1H), 3.41 (d, J = 4.4 Hz, 2H), 3.25 (bs, 4H).

IR (KBr, cm^{-1}): 3353, 3202, 3148, 3043, 2947, 2853, 1537, 1593, 1522, 1456, 1365, 1248, 1200, 1029, 982, 855, 770, 576.

CI-MS (m/z): 427(M^++1), 395, 369, 353, 308, 186, 142.

Example 15:

4-{4-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-[1,2,3]triazol-1-yl]-2-fluoro-phenyl}-piperazine-1-carboxylic acid *tert*-butyl ester



To a solution of 4-(4-azido-2-fluoro-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (10 grams, 31.15 mmol), obtained in preparation 17, *N*-ethyldiisopropyl amine (8.3 mL, 46.7 mmol) and propargyl phthalimide (6.4 grams, 34.3 mmol) in DMF (50 mL) was added cuprous iodide (3.25 grams, 15.58 mmol) in small batches at 25-35 °C and allowed to stir for 3 hours. Saturated ammonium chloride solution containing 10% ammonium hydroxide was added and stirred for 15 minutes. The aqueous layer was extracted with ethyl acetate (50 mL x 3) and the combined extracts were washed with water and brine successively and dried over sodium sulfate. Evaporation of volatiles left a residue, which was crystallized from 50% ethyl acetate: pet.ether system to get 15 grams of title compound (95%).

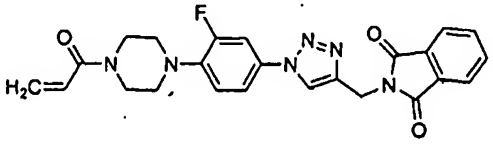
^{1}H NMR ($CDCl_3$): 7.96 (s, 1H), 7.83-7.90 (m, 2H), 7.71-7.77 (m, 2H), 7.27-7.50 (m, 2H), 6.99 (t, J = 8.7 Hz, 1H), 5.07 (s, 2H), 3.61 (t, J = 5.0 Hz, 4H), 3.07 (t, J = 4.9 Hz, 4H), 1.49 (bs, 9H).

IR (KBr, cm^{-1}): 3469, 1721, 1685, 1523, 1425, 1397, 1232.

CI-MS (m/z): 507, 451, 407.

Example 16:

2-{1-[4-(4-Acrolyl-piperazin-1-yl)-3-fluoro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl}-isoindole-1,3-dione



To 4-{4-[4-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-[1,2,3]triazol-1-yl]-2-fluoro-phenyl}-piperazine-1-carboxylic acid *tert*-butyl ester (2.9 grams, 4.94 mmol), obtained in example 15, was added trifluoro acetic acid (4 mL) and the resulting solution was stirred for 1 hour. Trifluoroaceticacid was evaporated and the residue formed was washed with ether. The solid obtained was dissolved in dichloromethane (20 mL) and trietheylamine (2.42 mL, 17.26 mmol) was added at ice temperature followed by the addition of acrolyl chloride (0.44 mL, 5.4 mmol). Upon stirring for 16 hours at 25-35 °C the reaction mixture was washed with water followed by brine. Evaporation of volatiles left a residue, which was passed through a silica gel column (60-120 mesh; eluent: ethyl acetate: pet. ether) to produce the title compound (2.0 grams, 44%).

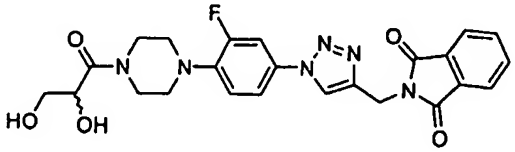
^{1}H NMR ($CDCl_3$): δ 7.97 (s, 1H), 7.84-7.90 (m, 2H), 7.71-7.77 (m, 2H), 7.38-7.52 (m, 2H), 6.99 (t, J = 8.8 Hz, 1H), 6.28-6.68 (m, 2H), 5.72-5.78 (dd, J = 2.0 & 10.2 Hz, 1H), 5.07 (s, 2H), 3.78-3.89 (m, 4H), 3.12-3.22 (m, 4H)

IR (KBr, cm^{-1}): 3427, 1723, 1152, 1085.

CI-MS (m/z): 503, 461, 142, 127.

Example 17:

2-(1-{4-[4-(2,3-Dihydroxy-propionyl)-piperzin-1-yl]-3-fluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-isoindole-1,3-dione



To a solution of 2-{1-[4-(4-acrolyl-piperazin-1-yl)-3-fluoro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl}-isoindole-1,3-dione (1.2 grams, 1.52 mmol), obtained in example 16, in 50% acetone : water (40 mL) were added *N*-methyl morpholine *N*-oxide (351 mg, 2.6 mmol) and 1% osmium tetroxide (66 mg, 0.26 mmol) in *tert*-butanol (6.6 mL) and stirred at 25-35 °C for 4 hours. The reaction mixture was extracted with ethyl acetate (50 mL x 2) and the combined organic layer was washed with brine and dried over sodium sulfate. Evaporation of volatiles left a residue, which was passed through a silica gel column (60-120 mesh; eluent, 1:9; methanol/chloroform) to produce the title compound (1.15 grams, 90%).

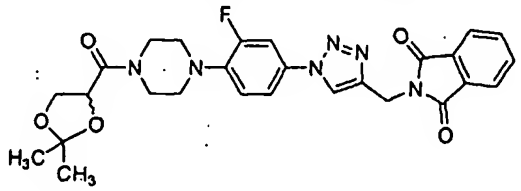
^{1}H NMR ($CDCl_3$): δ 8.37 (s, 1H), 7.77-7.90 (m, 2H), 7.52-7.62 (m, 2H), 7.06 (t, J = 8.7 Hz, 1H), 5.01 (s, 2H), 4.46-4.58 (m, 3H), 3.79 (bs, 4H), 3.67 (bs, 1H), 3.15 (bs, 4H).

IR (KBr, cm^{-1}): 3417, 2922, 1723, 1632, 1398, 1241, 529.

CI-MS (m/z): 503, 477, 435, 407.

Example 18:

2-(1-{4-[4-(2,2-Dimethyl-[1,3]dioxolane-4-carbonyl)-piperazin-1-yl]-3-fluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-isoindole-1,3-dione



To a solution of 2-(1-{4-[4-(2,3-dihydroxy-propionyl)-piperzin-1-yl]-3-fluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-isoindole-1,3-dione (750 mg, 1.52 mmol), obtained in example 17, in benzene (10 mL) were added 2,2-dimethoxy propane (317 mg, 3.04 mmol) and pyridinium-*p*-toluenesulphonate (50 mg) and refluxed for 2 hours. The reaction mixture was diluted with ethyl acetate (50 mL) followed by the addition of triethylamine (0.5 mL). Usual washings with water and brine and evaporation of the volatiles produced the title compound (550 mg, 73%).

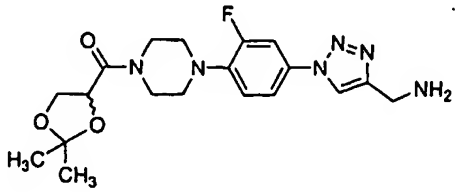
^{1}H NMR ($CDCl_3$): δ 7.96 (s, 1H), 7.84-7.89 (m, 2H), 7.70-7.74 (m, 2H), 7.37-7.50 (m, 2H), 6.99 (t, J = 8.7 Hz, 1H), 5.06 (s, 2H), 4.7 (t, J = 6.4 Hz, 1H), 4.49 (t, J = 8.3 Hz, 1H), 4.14 (t, J = 8.1 Hz, 1H), 4.06-3.68 (m, 4H), 3.11 (m, 4H), 1.41 (s, 6H).

IR (KBr, cm^{-1}): 3443, 2925, 2854, 1718, 1649, 1521, 1237, 1046, 715, 532.

CI-MS (m/z): 535, 272, 254, 224, 118.

Example 19:

{4-[4-(4-Aminomethyl-[1,2,3]triazol-1-yl)-2-fluoro-phenyl]-piperazin-1-yl}-(2,2-dimethyl-[1,3]dioxolan-4-yl)methanone



To a solution of 2-(1-{4-[4-(2,2-dimethyl-[1,3]dioxolane-4-carbonyl)-piperazin-1-yl]-3-fluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-isoindole-1,3-dione (500 mg, 0.936 mmol), obtained in example 18, in methanol (10 mL) was added hydrazine hydrate (0.3 mL) and refluxed for 4 hours. Removal of methanol by distillation left a residue, which was triturated with ether (50 mL x 3) and the combined ether layer was washed with water and brine successively. Evaporation of the ether gave 350 mg (93%) of product.

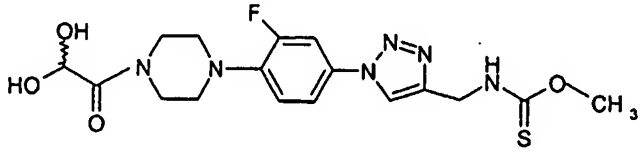
^{1}H NMR ($CDCl_3$): δ 8.43 (s, 1H), 7.49-7.71 (m, 2H), 7.09 (t, J = 8.9 Hz, 1H), 4.78 (t, J = 6.1 Hz, 1H), 4.42 (t, J = 6.4 Hz, 1H), 3.34 (s, 4H), 3.19 (bs, 4H), 1.48 (s, 6H).

IR (KBr, cm^{-1}): 3439, 2925, 1649, 1523, 1239, 1065, 866.

CI-MS (m/z): 405, 391, 364, 283, 179, 147.

Example 20:

(1-{4-[4-(2,3-Dihydroxy-propionyl)-piperazin-1-yl]-3-fluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester



To a solution of {4-[4-(4-aminomethyl-[1,2,3]triazol-1-yl)-2-fluoro-phenyl]-piperazin-1-yl}-(2,2-dimethyl-[1,3]dioxalan-4-yl)methanone (350 mg, 0.87 mmol), obtained in example 19, in chloroform (10 mL) were added saturated sodium bicarbonate solution (10 mL) followed by the addition of thiophosgene (0.066 mL) at ice temperature and stirred for 2 hours. Organic layer was separated and aqueous layer was extracted with chloroform. Combined organic phases were washed with brine and dried over sodium sulfate. Evaporation of the volatiles gave a residue, which was diluted with methanol (10 mL) and refluxed for 16 hours. Methanol was evaporated and the residue formed was

passed through a silica gel column (60-120 mesh; eluent: 1:9, methanol/chloroform) to give 300 mg (79%) of the title compound.

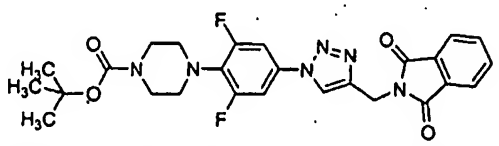
^{1}H NMR ($CDCl_3$): δ 8.05 & 7.82 (2s, rotamers in 4:1 ratio, 1H), 7.5 (d, J = 12.6 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.03 (bs, 1H), 7.01 (t, J = 8.6 Hz, 1H), 4.91 & 4.66 (2d, raotamers in 4:1 ratio, J = 6.2 Hz, 2H) 4.52 (bs, 1H), 4.12 & 3.99 (2s, rotamers in 1:4 ratio, 3H), 3.92-3.69 (m, 7H), 3.14 (bs, 4H), 2.57 (bs, 4H).

IR (KBr, cm^{-1}): 3425, 2924, 1635, 1522, 1455, 1230, 1145, 1027, 864, 817, 696.

CI-MS (m/z): 435, 389, 373, 347, 319, 294, 277, 238, 206, 187, 174, 137, 102, 93.

Example 21:

4-{4-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-[1,2,3]triazol-1-yl]-2,6-difuoro-phenyl}-piperazine-1-carboxylic acid *tert*-butyl ester



The title compound was prepared from 4-(4-azido-2,6-difluoro-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester, obtained from preparation 18, and propargyl phthalimide following the same procedure as described for the preparation of 4-{4-[4-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-[1,2,3]triazol-1-yl]-2-fluoro-phenyl}-piperazine-1-carboxylic acid *tert*-butyl ester (Example 15).

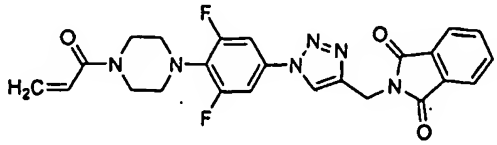
^{1}H NMR ($CDCl_3$) : δ 7.95 (s, 1H), 7.89-7.85 (m, 2H), 7.75-7.71 (m, 2H), 7.27 (d, J = 8.9 Hz, 2H), 5.06 (s, 2H), 3.55-3.53 (m, 4H), 3.17-2.96 (m, 4H), 1.68 (s, 9H).

IR (KBr, cm^{-1}) : 2924, 1716, 1522, 1397.

CI-MS : 525 (M++1), 469, 425, 314, 258, 148, 105.

Example 22:

2-{1-[4-(4-Acrolyl-piperazin-1-yl)-3,5-difluoro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl}-isoindole-1,3-dione



Title compound (2.4 grams, 88%) was prepared from 4-{4-[4-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-[1,2,3]triazol-1-yl]-2,6-fluoro-phenyl}-piperazine-1-carboxylic acid *tert*-butyl ester (3.0 grams, 5.73 mmol), obtained in example 21, acroloyl

chloride (0.51 mL, 6.3 mmol) and triethyl amine (2.4 mL, 17.2 mmol) following the same procedure as descibed for the prepration of 2-{1-[4-(4-acrolyl-piperazin-1-yl)-3-fluoro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl}-isoindole-1,3-dione (Example 16).

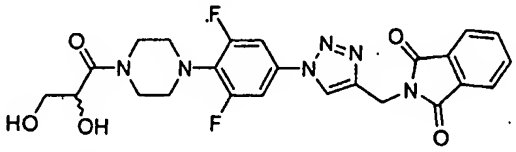
^{1}H NMR ($CDCl_3$): δ 7.96 (s, 1H), 7.89-7.71 (m, 4H), 7.28 (d, J = 9.1 Hz, 2H), 6.64 & 6.56 (2d, J = 10.5 Hz, 1H), 6.32 (d, J = 16.9 Hz, 1H), 5.73 (d, J = 10.2 Hz, 1H), 5.06 (s, 2H), 3.81 (bs, 2H), 3.69 (bs, 2H), 3.23 (bs, 4H).

IR (KBr, cm^{-1}): 3439, 3085, 2853, 1719, 1644, 1518, 1465, 1438, 1395, 1231, 1032, 856, 715, 530.

CI-MS (m/z): 479 (M^++1), 450, 425, 366, 297, 211, 194, 165, 121, 92.

Example 23:

2-(1-{4-[4-(2,3-Dihydroxy-propionyl)-piperzin-1-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-isoindole-1,3-dione



Title compound (1.0 gram, 47%) was prepared from 2-{1-[4-(4-acrolyl-piperazin-1-yl)-3,5-difluoro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl}-isoindole-1,3-dione (2.0 grams, 4.2 mmol), obtained in example 22, 1% osmiumtetroxide in *tert*-butanol (107 mg, 0.42 mmol) and *N*-methyl morpholine-*N*-oxide (567 mg, 4.2 mmol) following the same procedure as described for the preparation of 2-(1-{4-[4-(2,3-dihydroxy-propionyl)-piperzin-1-yl]-3-fluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-isoindole-1,3-dione (Example 17).

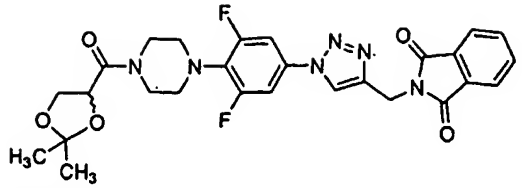
^{1}H NMR ($CDCl_3$): δ 7.96 (s, 1H), 7.90-7.72 (m, 4H), 7.29 (d, J = 11.8 Hz, 2H), 5.07 (s, 2H), 4.49-4.48 (m, 1H), 3.81-3.62 (m, 6H), 3.25 (bs, 4H).

IR (KBr, cm^{-1}): 3416, 1718, 1637, 1519, 1467, 1396, 1279, 1232, 1211, 1027, 939, 855, 715, 530.

CI-MS (m/z): 513 (M^++1), 483, 425, 315, 287, 229, 163, 91.

Example 24:

2-(1-{4-[4-(2,2-Dimethyl-[1,3]dioxolane-4-carbonyl)-piperazin-1-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-isoindole-1,3-dione



Title compound (0.9 gram, 83%) was obtained from 2-(1-{4-[4-(2,3-dihydroxy-propionyl)-piperzin-1-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-isoindole-1,3-dione (1.0 gram, 1.95 mmol), obtained in example 23, 2,2-dimethoxy propane (0.5 mL, 3.91 mmol) and pyridinium *p*-tolunesulfonate (50 mg, 0.195 mmol) following the same procedure as described for the preparation of 2-(1-{4-[4-(2,2-dimethyl-[1,3]dioxolane-4-carbonyl)-piperazin-1-yl]-3-fluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-isoindole-1,3-dione (Example 18).

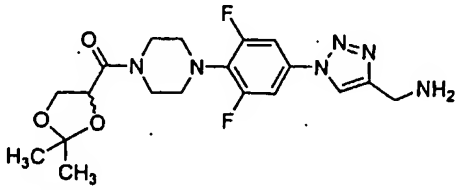
^{1}H NMR ($CDCl_3$): δ 7.96 (s, 1H), 7.90-7.72 (m, 4H), 7.29 (d, J = 11.8 Hz, 2H), 5.07 (s, 2H), 4.49-4.48 (m, 1H), 3.81-3.62 (m, 6H), 3.25 (bs, 4H).

IR (KBr, cm^{-1}): 3416, 1718, 1637, 1519, 1467, 1396, 1279, 1232, 1211, 1027, 939, 855, 715, 530.

CI-MS (m/z): 513 (M^++1), 483, 425, 315, 287, 229, 163, 91.

Example 25:

{4-[4-(4-Aminomethyl-[1,2,3]triazol-1-yl)-2,6-difluoro-phenyl]-piperazin-1-yl}-(2,2-dimethyl-[1,3]dioxalan-4-yl)methanone



Title compound (550 mg, 80%) was prepared from 2-(1-{4-[4-(2,2-dimethyl-[1,3]dioxolane-4-carbonyl)-piperazin-1-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-isoindole-1,3-dione (900 mg, 1.62 mmol), obtained in example 24, and hydrazine hydrate (0.5 mL) following the procedure as described for the preparation of {4-[4-(4-aminomethyl-[1,2,3]triazol-1-yl)-2-fluoro-phenyl]-piperazin-1-yl}-(2,2-dimethyl-[1,3]dioxalan-4-yl)methanone (Example 19).

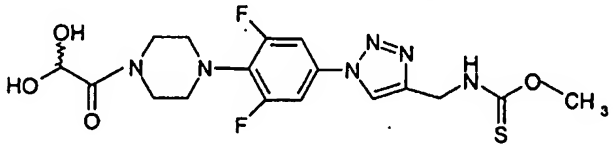
^{1}H NMR ($CDCl_3$): δ 7.84 (s, 1H), 7.33 (d, J = 9.3 Hz, 2H), 4.72 (t, J = 6.2 Hz, 1H), 4.51 (dd, J = 8.3 Hz & 5.8 Hz, 1H), 4.16 (dd, J = 8.3 Hz & 6.8 Hz, 1H), 4.07 (s, 1H), 3.94-3.63 (m, 4H), 3.24 (d, J = 4.6 Hz), 1.43 (d, J = 1.9 Hz, 6H).

IR (KBr, cm^{-1}): 3442, 2988, 2924, 2856, 1844, 1520, 1460, 1381, 1279, 1230, 1154, 1038, 1001, 933, 855, 701, 616, 565, 533.

CI-MS (m/z): 423 (M^++1), 365, 342, 320, 265, 236, 407, 192, 163, 101, 91.

Example 26:

(1-{4-[4-(2,3-Dihydroxy-propionyl)-piperazin-1-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester



Title compound (270 mg, 45%) was prepared from {4-[4-(4-aminomethyl-[1,2,3]triazol-1-yl)-2,6-difluoro-phenyl]-piperazin-1-yl}-(2,2-dimethyl-[1,3dioxalan-4-yl)methanone (550 mg, 1.3 mmol), obtained in example 25, using thiophosgene (115 mL, 1.43 mmol) and sodium bicarbonate (1.1 grams, 13 mmol) following the same procedure as described for the preparation of (1-{4-[4-(2,3-dihydroxy-propionyl)-piperazin-1-yl]-3-fluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester (Example 20).

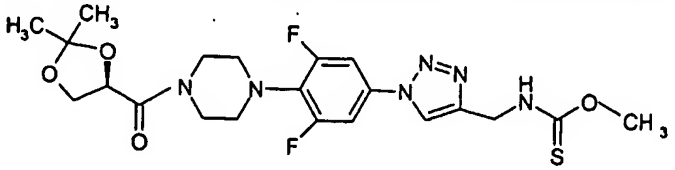
^{1}H NMR ($CDCl_3$): δ 8.07 & 7.81 (2s, rotamers in 4:1 ratio, 1H), 7.32 (d, J = 9.3 Hz, 2H), 6.96 (bs, 1H), 4.91 & 4.65 (2d, rotamers in 4:1 ratio, J = 5.9 Hz, 2H), 4.51 (bs, 1H), 4.12 & 4.00 (2s, rotamers in 1:4 ratio, 3H), 3.92-3.63 (m, 7H), 3.25 (bs, 4H), 2.50 (bs, 1H).

IR (KBr, cm^{-1}): 3262, 3012, 2947, 2858, 1635, 1519, 1457, 1389, 1334, 1278, 1231, 1149, 1118, 1096, 1029, 857, 756.

CI-MS (m/z): 457 (M^++1), 425, 369, 320, 295, 245, 207, 183, 157, 128, 91.

Example 27:

(*R*)-(1-{4-[4-(2,2-dimethyl-[1,3]dioxolane-4-carbonyl)-piperazin-1-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid *O*-methyl ester



To a solution of (*R*)-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid (876 mg, 6.0 mmol), obtained in preparation 29, in DCM (15 mL) were added 1-(3,5-difluoro-4-piperazin-1-yl-phenyl)-1*H*-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid *O*-methyl ester

(2.0 grams, 5.43 mmol), obtained in example 6, and *N*-methyl morpholine (604 mg, 6.0 mmol) at 0 °C *N*-(3-dimethylaminopropyl)-*N'*-ethyl carbodiimide hydrochloride (1.15 grams, 6.0 mmol) was added to the reaction mixture portion wise and stirring was continued at 0 °C for additional 1 hour and then at 25-35 °C 9 to 13 hours. Reaction mixture was then diluted with ethyl acetate (250 mL) and the organic portion was washed with water followed by brine and dried over sodium sulfate. Removal of volatiles and purification of the resulting residue by column chromatography (methanol/chloroform, 1:9) yielded the title compound (2.17 grams, 75%).

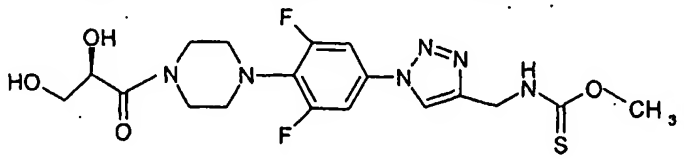
^{1}H NMR ($CDCl_3$) : δ 8.06 & 7.81 (2s, rotamers in ratio of 4:1, 1H), 7.31 (d, J = 9.3 Hz, 2H), 6.91 (bs, 1H), 4.90 (d, J = 6.2 Hz, 2H), 4.71-4.68 (m, 1H), 4.41-4.61 (m, 1H), 4.15-4.11 (m, 1H), 3.99 (s, 3H), 3.69-3.85 (m, 4H), 3.10-3.30 (m, 4H), 1.42 (s, 6H).

IR (KBr, cm^{-1}) : 3248, 1631, 1519, 1372.

CI-MS : 497 (M++1), 465, 433, 408, 380, 280.

Example 28:

(1-{4-[4-(2(*R*),3-Dihydroxy-propionyl)-piperazin-1-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester



To an ice-cooled suspension of (*R*)-(1-{4-[4-(2,2-dimethyl-[1,3]dioxolane-4-carbonyl)-piperazin-1-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl] thiocarbamic acid *O*-methyl ester (3.3 grams, 6.65 mmol), obtained in example 27, in methanol (25 mL) was added 50% aqueous HCl (25 mL) drop wise and stirred at 25-35 °C for 9 to 13 hours. Reaction mixture was diluted with water (30 mL) and then cooled to ice temp. pH of the reaction mixture was brought to 7 by the addition of solid sodium bicarbonate and extracted with chloroform. Combined organic portions were dried over sodium sulfate and the residue obtained after removal of volatiles was purified by column chromatography (silica gel 60-120, eluent; methanol/chloroform, 3: 97) to get the title compound (1.75 grams, 58%).

^{1}H NMR ($CDCl_3$): δ 8.06 & 7.82 (2s, rotamers in 4:1 ratio, 1H), 7.32 (d, J = 9.1 Hz, 2H), 6.99 (bs, 1H), 4.91 & 4.65 (2d, rotamers in 4:1 ratio, J = 5.9 Hz, 2H), 4.51 (dd, J = 6.2 &

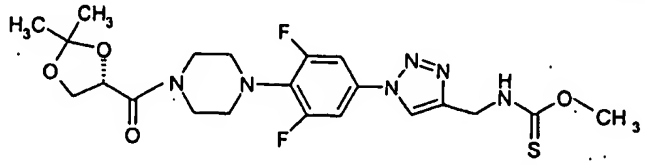
9.7 Hz, 1H), 4.10 & 3.99 (2s, rotamers in 1:4 ratio, 3H), 3.92-3.64 (m, 7H), 3.25 (bs, 4H), 2.53 (bs, 1H)

IR (KBr, cm^{-1}): 3266, 1638, 1519, 1463, 1278, 1203, 1026, 853, 736.

CI-MS (m/z): 457 (M^++1), 425, 393, 383, 369, 340, 302, 280, 268, 238, 195, 165, 123, 106, 92.

Example 29:

(*S*)-(1-{4-[4-(2,2-dimethyl-[1,3]dioxolane-4-carbonyl)-piperazin-1-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid *O*-methyl ester



To a solution of (*S*)-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid (890 mg, 6.1 mmol), obtained from the corresponding methyl ester, in THF (20 mL) was added triethyl amine (2.12 mL, 15 mmol) followed by the addition of isobutylchloroformate (0.8 mL, 6.1 mmol) at ice temperature and stirring was continued for 20 minutes. A solution of 1-(3,5-difluoro-4-piperazin-1-yl-phenyl)-1*H*-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid *O*-methyl ester (1.86 grams, 5.0 mmol), obtained in example 6, in THF (10 mL) was then added to the above reaction mixture and it was further stirred 9 to 13 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. Combined ethyl acetate extract was washed with water followed by brine and dried over sodium sulfate. Removal of volatiles and purification of the resulting residue by column chromatography (methanol/chloroform, 1:9) yielded the title compound (700 mg, 30%).

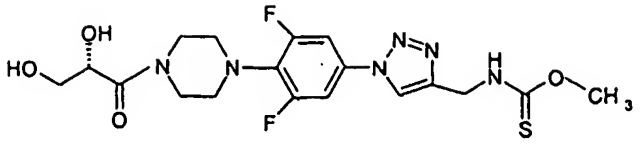
^{1}H NMR ($CDCl_3$) : δ 8.05 & 7.81 (2s, rotamers in ratio of 4:1, 1H), 7.34-7.28 (m, 2H), 6.91 (bs, 1H), 4.91 & 4.65 (d, J = 6.0 Hz, rotamers in ratio of 4:1, 2H), 4.70 (t, J = 6.3 Hz, 1H), 4.53-4.49 (m, 1H), 4.17-4.11 (m, 1H), 4.01 (s, 3H), 3.60-3.91 (m, 4H), 3.10-3.30 (m, 4H), 1.41 (s, 6H).

IR (KBr, cm^{-1}) : 3250, 1632, 1522, 1205.

CI-MS : 497 (M^++1), 465, 433, 408, 380, 280.

Example 30:

(1-{4-[4-(2(*S*),3-Dihydroxy-propionyl)-piperazin-1-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester:



Title compound (0.8 gram, 27%) was obtained from (*S*)-(1-{4-[4-(2,2-dimethyl-[1,3]dioxolane-4-carbonyl)-piperazin-1-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid *O*-methyl ester (3.2 grams, 8.72 mmol), obtained in example 29, following the same procedure as described for the preparation of (1-{4-[4-(2(*R*),3-dihydroxy-propionyl)-piperazin-1-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester (Example 28).

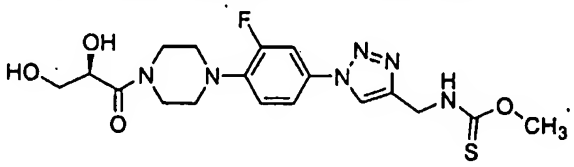
^{1}H NMR ($CDCl_3$): δ 8.07 & 7.83 (2s, rotamers in 4:1 ratio, 1H), 7.31 (d, *J* = 9.1 Hz, 2H), 7.11 (t, *J* = 5.4 Hz, 1H), 4.91 & 4.65 (2d, rotamers in 4:1 ratio, *J* = 5.9 Hz, 2H), 4.51 (bs, 1H), 4.11 & 3.99 (2s, rotamers in 1:4 ratio, 3H), 3.96-3.64 (m, 7H), 3.25 (bs, 4H), 2.65 (bs, 1H).

IR (KBr, cm^{-1}): 3240, 3129, 2942, 2857, 1740, 1634, 1518, 1461, 1399, 1336, 1277, 1202, 1055, 1026, 851, 694.

CI-MS (m/z): 457 (M^++1), 425, 407, 383, 369, 340, 302, 169, 106, 92.

Example 31:

(1-{4-[4-(2(*R*),3-Dihydroxy-propionyl)-piperazin-1-yl]-3-fluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester:



The title compound was synthesized from [1-(3-fluoro-4-piperazin-1-yl-phenyl)-1*H*-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid *O*-methyl ester, obtained in example 5, following the same procedure as described for the preparation of (1-{4-[4-(2(*R*),3-dihydroxy-propionyl)-piperazin-1-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester (Example 28).

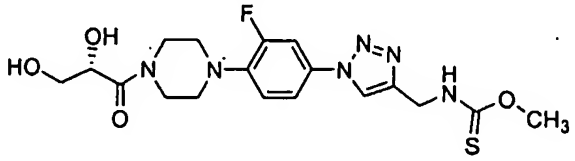
^{1}H NMR (DMSO-d_6) : δ 9.64-9.59 (m, 1H), 8.64 & 8.60 (2s, rotamers in ratio of 4:1, 1H), 7.79 (dd, *J* = 8.1 & 2.4 Hz, 1H), 7.68 (dd, *J* = 6.2 & 1.6 Hz, 1H), 7.22 (t, *J* = 9.1 Hz, 1H), 4.96 (d, *J* = 5.4 Hz, 1H), 4.72 & 4.44 (2d, rotamers in ratio of 4:1, *J* = 5.6 Hz, 2H), 4.70 (bs, 1H), 4.38 (d, *J* = 4.6 Hz, 1H), 3.95 & 3.89 (2s, rotamers in ratio of 1:4, 3H), 3.72-3.69 (m, 2H), 3.58-3.49 (m, 2H), 3.08 (s, 4H).

IR (KBr, cm^{-1}) : 3457, 1727, 1628, 1526.

CI-MS : 439 (M^++1), 389, 291, 181, 108.

Example 32:

(1-{4-[4-(2(*S*),3-Dihydroxy-propionyl)-piperazin-1-yl]-3-fluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester:



The title compound was synthesized from (*S*)-(1-{4-[4-(2,2-dimethyl-[1,3]dioxolane-4-carbonyl)-piperazin-1-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid *O*-methyl ester, obtained in example 29, following the same procedure as described for the preparation of (1-{4-[4-(2(*S*),3-dihydroxy-propionyl)-piperazin-1-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester (Example 30).

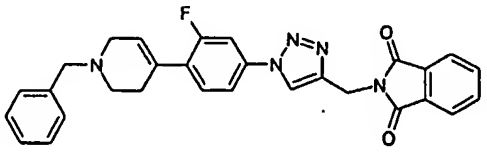
^{1}H NMR ($CDCl_3$+DMSO-d_6) : δ 9.10 (s, 1H), 8.25 & 8.10 (2s, rotamers in ratio of 4:1, 1H), 7.20-7.61 (m, 2H), 7.07 (t, J = 8.8 Hz, 1H), 4.83 & 4.56 (2d, rotamers in ratio of 4:1, J = 5.7 Hz, 2H), 4.41-4.59 (m, 3H), 4.04 & 3.97 (2s, rotamers in ratio of 1:4, 3H), 3.79-3.69 (m, 4H), 3.16-3.06 (m, 4H).

IR (KBr, cm^{-1}) : 3226, 1624, 1523, 1442, 1233, 1049.

CI-MS : 439 (M^++1), 389, 351, 319, 195, 102.

Example 33:

2-{1[4-Benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)-3-fluoro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl isoindole-1,3-dione :



To a solution of 4-(4-azido-2-fluoro-phenyl)-1-benzyl-1,2,3,6-tetrahydro-pyridine (100 mg, 0.324 mmol), obtained in preparation 24, in acetonitrile (10 mL) was added N-Ethyldiisopropylamine (0.11 mL, 0.64 mmol) followed by the addition of 2-prop-2-ynyl-isoindole-1,3-dione (0.09 grams, 0.48 mmol), obtained in preparation 2, and cuprous

iodide (0.067 grams, 0.35 mmol) and stirred at 25-35 °C for 2 hours. The reaction mixture was filtered through a celite bed, which was washed thoroughly with 10% methanol in chloroform. The filtrates were concentrated under vacuum and the crude product was purified by silica gel column chromatography (50% ethyl acetate/pet. ether) to get desired product as a yellow solid (150 mg, 93%).

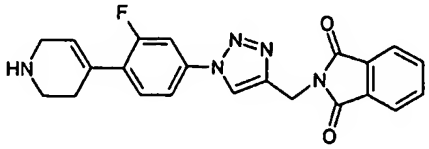
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.01 (s, 1H), 7.93-7.80 (m, 2H), 7.80-7.64 (m, 2H), 7.52-7.19 (m, 8H), 6.11-6.00 (m, 1H), 5.07 (s, 2H), 3.65 (s, 2H), 3.28-3.10 (m, 2H), 2.80-2.62 (m, 2H), 2.62-2.44 (m, 2H)

IR (KBr): 3434, 2925, 1721, 1393 cm^{-1}

CI-MS (m/e): 494 (M^++1), 408, 400

Example 34:

2-{1-[3-Fluoro-4-(1,2,3,6-tetrahydro-pyridin-4-yl)-phenyl]-1*H*-[1,2,3]triazol-4-yl methyl}- isoindole-1,3-dione



To a solution of 2-{1[4-Benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)- 3-fluoro-phenyl]-1*H*- [1,2,3] triazole-4-ylmethyl isoindole-1,3-dione (300 mg, 0.608 mmol), obtained in example 33, in dry dichloromethane (10 mL) at 0 °C added drop wise 1-chloroethyl chloroformate (0.067 mL, 0.611 mmol) and allowed the reaction mixture to stir at the same temperature for 1.5 hours. Evaporated the solvent on rotavapor and dissolved the residue in methanol (20 mL). Refluxed the reaction mixture for 0.5 hours. The solvent was evaporated and the residue was purified by silica gel column chromatography (5 % methanol/chloroform) to get the desired product as a white solid (150 mg, 61%).

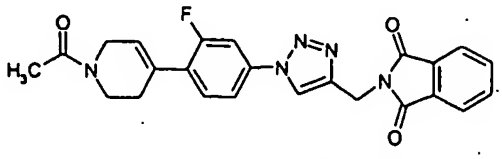
^{1}H NMR (DMSO-d_6 + MeOH-d_4, 200 MHz): δ 8.70 (s, 1H), 7.99-7.72 (m, 6H), 7.60 (t, *J* = 8 Hz, 1H), 6.16-6.13 (m, 1H), 5.00 (s, 2H), 3.92-3.72 (m, 2H), 3.39 (t, *J* = 6.1 Hz, 2H), 2.84-2.64 (m, 2H)

IR (KBr): 3435, 2925, 1711, 1618, 1396 cm^{-1}

CI-MS (m/e): 403 (M^++1)

Example 35:

2-{1-[4-(1-Acetyl-1,2,3,6-tetrahydro-pyridin-4-yl)-3-fluoro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl}-isoindole-1,3-dione



To a solution of 2-{1-[3-fluoro-4-(1,2,3,6-tetrahydro-pyridin-4-yl)-phenyl]-1*H*-[1,2,3]triazol-4-yl methyl}-isoindole-1,3-dione (150 mg, 0.372 mmol), obtained in example 34, in dry dichloromethane (10 mL), added triethylamine (0.103 mL, 0.744 mmol) followed by the addition of acetyl chloride (0.029 mL, 0.409 mmol) and 4-dimethylaminopyridine (5 mg, 0.037 mmol) and allowed the reaction mixture to stir for 10 hours at 25-35 °C. Solvent was evaporated and the residue purified by silica gel column chromatography (70 % ethyl acetate/pet. ether) to yield desired product as white solid (100 mg, 61%).

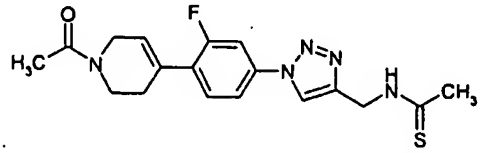
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.03 (s, 1H), 7.96-7.80 (m, 2H), 7.80-7.67 (m, 2H), 7.55-7.30 (m, 3H), 6.10-5.98 (m, 1H), 5.07 (s, 2H), 4.35-4.20 (m, 1H), 4.20-4.08 (m, 1H), 3.81 (t, J = 5.6 Hz, 1H), 3.66 (t, J = 5.6 Hz, 1H), 2.72-2.42 (m, 2H), 2.17 (s, 3H)

CI-MS (m/e): 446 (M^++1)

IR (KBr): 3453, 2924, 1710, 1651, 1459 cm^{-1}

Example 36:

***N*-{1-[4-(1-Acetyl-1, 2, 3, 6-tetrahydro-pyridin-4-yl)-3-fluoro-phenyl]-1*H*-[1, 2, 3] triazol-4-ylmethyl}-thioacetamide**



To 2-{1-[4-(1-acetyl-1,2,3,6-tetrahydro-pyridin-4-yl)-3-fluoro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl}-isoindole-1,3-dione (100 mg, 0.224 mmol), obtained in example 35, in methanol (20 mL) was added hydrazine hydrate (0.096 mL) and refluxed the reaction mixture for 2 hours. Concentrated the reaction mixture and residue obtained was purified by silica gel column chromatography (5% methanol/chloroform) to yield 1-{4-[4-(4-aminomethyl-[1,2,3]triazol-1-yl)2-fluoro-phenyl]-3,6-dihydro-2*H*-pyridin-1-yl}-ethanone as a white solid (65 mg). Then it was dissolved in THF (5 mL), cooled to 0 °C

was added triethylamine (0.057 mL, 0.412 mmol) followed by the addition of ethyl dithioacetate (0.03 mL, 0.267 mmol). The reaction mixture was brought to 25-35 °C and stirred for 12 hours. Evaporated the solvent on rotavapor and purified the residue by silica gel column chromatography (80 % ethyl acetate/pet.ether) to yield the desired product as a white solid (70 mg, 89%).

Melting Point: 132-135 °C.

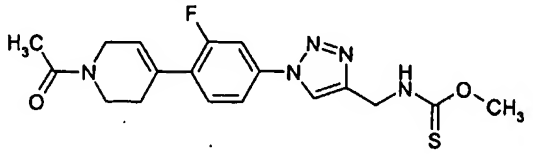
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12 (s, 2H), 7.58-7.42 (m, 2H), 7.41-7.35 (m, 1H), 6.08-6.01 (m, 1H), 5.00 (d, J = 5 Hz, 2H), 4.30- 4.22 (m, 1H), 4.18-4.14 (m, 1H), 3.86-3.78 (m, 1H), 3.72-3.60 (m, 1H), 2.60 (s, 3H), 2.64-2.52 (m, 2H), 2.16 (s, 3H)

IR (KBr): 3446, 2924, 2853, 1623, 1461 cm^{-1}

CI-MS (m/e): 374 (M^++1)

Example 37:

{1-[4-(1-Acetyl-1,2,3,6-tetrahydro-pyridin-4-yl)-3-fluoro-phenyl]-1H-[1,2,3] triazol-4-ylmethyl}-thiocarbamic acid O-methyl ester



To a solution of 1-{4-[4-(4-Aminomethyl-[1,2,3]triazol-1-yl)2-fluoro-phenyl]-3,6-dihydro-2*H*-pyridin-1-yl}-ethanone (0.1 gram, 0.317 mmol), in THF (5 mL) was added triethylamine (0.09 mL, 0.634 mmol) and brought the reaction temperature down to 0 °C. To this solution was added carbon disulphide (0.023 mL, 0.38 mmol) and allowed the reaction mixture to stir at the same temperature for 4 hours, after which ethylchloroformate (0.032 mL, 0.348 mmol) was added and the reaction was continued for another 1 hour at 0 °C. The solvent was evaporated and methanol (8 mL) was added to the residue and the reaction mixture was refluxed for 12 hours. Methanol was removed by evaporation and the residue was purified by silica gel column chromatography (70 % ethyl acetate/pet.ether) to afford the desired product as white solid (100 mg, 81%).

Melting Point: 155-157 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12 and 7.84 (two s, 1H, rotamers in ratio of 4:1), 7.58-7.44 (m, 2H), 7.42-7.38 (m, 1H), 6.94-6.86 (m, 1H), 6.08-6.00 (m, 1H), 4.93 and 4.68 (two d, J = 5.8 Hz, 2H, rotamers in the ratio of 4:1), 4.32-4.28 (m, 1H), 4.20-4.12 (m, 1H),

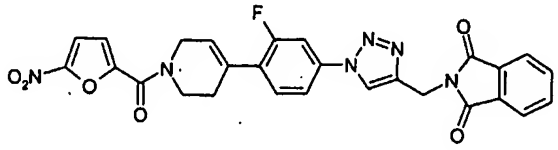
4.00 (s, 3H), 3.82 (t, J = 5.3 Hz, 1H), 3.68 (t, J = 5.3 Hz, 1H), 2.64-2.52 (m, 2H), 2.18 (s, 3H)

IR (KBr): 3184, 2925, 1634, 1515, 1429, 1240 cm^{-1}

CI-MS (m/e): 390 (M^++1), 358

Example 38:

2-(1-{3-Fluoro-4-[1-(5-nitro-furan-2-carbonyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-isoindole-1,3-dione :



To a solution of 2-{1-[3-fluoro-4-(1,2,3,6-tetrahydro-pyridin-4-yl)-phenyl]-1*H*-[1,2,3]triazol-4-yl methyl}-isoindole-1,3-dione (1 gram, 2.48 mmol), obtained in example 34, in dry dichloromethane (15 mL) was added triethylamine (1.04 mL, 7.44 mmol) and cooled the reaction mixture to 0 °C . At this temperature added 2-nitro-5-furoyl chloride (0.52 grams, 2.97 mmol) to the reaction mixture and left it to stir at 25-35 °C for 12 hours.

The reaction mixture was diluted with dichloromethane (50 mL) washed with water followed by brine and dried over anhydrous sodium sulphate. The volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography (70 % ethyl acetate/pet.ether) to yield the titled compound as a yellow solid (1 gram, 75%)

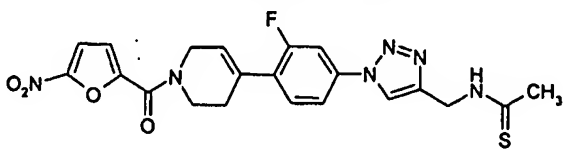
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.04 (s, 1H), 7.96-7.80 (m, 2H), 7.80-7.65 (m, 2H), 7.58-7.30 (m, 5H), 6.18-6.00 (m, 1H), 5.09 (s, 2H), 4.64-4.50 (m, 1H), 4.50-4.32 (m, 1H), 4.14- 3.92 (m, 2H), 2.84-2.72 (m, 2H)

IR (KBr): 3436, 2924, 1717, 1631 cm^{-1}

CI-MS (m/e): 543 (M^++1), 513, 494, 400

Example 39:

***N*-(1-{3-Fluoro-4-[1-(5-nitro-furan-2-carbonyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thioacetamide :**



To a solution of 2-(1-{3-fluoro-4-[1-(5-nitro-furan-2-carbonyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-isoindole-1,3-dione (1 gram, 1.84 mmol), obtained in example 38, in methanol (20 mL) was added hydrazine hydrate (0.79 mL) and refluxed the reaction mixture for 2 hours. Allowed the reaction mixture to stir for 12 hours at 25-35 °C. Evaporated the solvent and the residue was purified by silica gel column chromatography (10 % methanol/chloroform) to furnish 1-{4-[4-(4-aminomethyl-[1,2,3]triazol-1-yl)2-fluoro-phenyl]-3,6-dihydro-2*H*-pyridin-1-yl}-(5-nitro-furan-2-yl)-methanone as a white solid (640 mg) which was pure enough to carry out further step. Then a solution this amine (150 mg, 0.364 mmol) in THF (10 mL) was cooled to 0 °C, added triethylamine (0.101 mL, 0.728 mmol) followed by addition of ethyl dithioacetate (0.054 mL, 0.473 mmol). Allowed the reaction mixture to stir at 25-35 °C for 12 hours. Solvent was removed under vacuum and the residue was purified by silica gel column chromatography (70 % ethyl acetate/pet.ether) to get desired compound as a yellow solid (60 mg, 35%)

Melting Point : 112-114 °C.

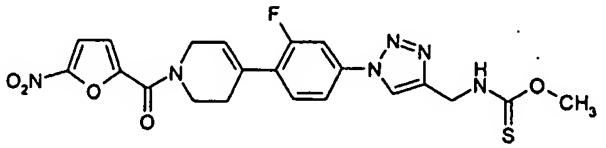
^{1}H NMR ($CDCl_3$+DMSO-d_6, 200 MHz): δ 10.24-10.10 (m, 1H), 8.37 (s, 1H), 7.70-7.54 (m, 2H), 7.54-7.40 (m, 2H), 7.24 (d, J = 3.6 Hz, 1H), 6.21-6.04 (m, 1H), 4.98 (d, J = 5.37 Hz, 2H), 4.68-4.34 (m, 2H), 4.12-3.92 (m, 2H), 2.86-2.62 (m, 2H), 2.55 (s, 3H).

IR (KBr): 3441, 2924, 1631, 1502, 1429, 1353 cm^{-1}

ES-MS (m/e): 471 (M+1)

Example 40:

(1-{3-Fluoro-4-[1-(5-nitro-furan-2-carbonyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester



To an ice cooled solution of 1-{4-[4-(4-aminomethyl-[1,2,3]triazol-1-yl)2-fluoro-phenyl]-3,6-dihydro-2*H*-pyridin-1-yl}-(5-nitro-furan-2-yl)-methanone (220 mg, 0.533 mmol), in dry THF (10 mL) was added triethylamine (0.09 mL, 0.639 mmol) and carbon disulphide (0.064 mL, 1.066 mmol) and allowed the reaction mixture to stir at 0 °C for 4 hours, after which ethyl chloroformate (0.049 mL, 0.533 mmol) was added and the

reaction was continued for another 1 hour at 0 °C. The solvent was evaporated and methanol (20 mL) was added to the residue and the reaction mixture was refluxed for 12 hours. Methanol was removed by evaporation and the residue was purified by silica gel column chromatography (3% methanol/chloroform) to get the desired compound as a white solid (90 mg, 35%).

Melting Point : 164-166 °C.

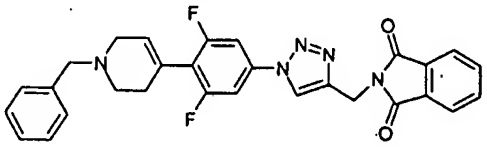
^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.71-9.60 (m, 1H), 8.75 and 8.72 (two s, 1H, rotamers in a ratio of 4:1), 7.89 (dd, J = 1.9 and 12.2 Hz, 1H), 7.84- 7.76 (m, 2H), 7.61 (t, J = 8.3 Hz, 1H), 7.38-7.34 (m, 1H), 6.24- 6.08 (m, 1H). 4.74 (d, J = 5.8 Hz, 2H), 4.56-4.40 (m, 2H), 4.39- 4.20 (m, 1H), 3.98-3.81 (m, 1H), 3.95 and 3.89 (two s, 3H, rotamers in a ratio 1:3), 2.76-2.52 (m, 2H).

IR (KBr): 3281, 2925, 1623, 1516, 1435, 1354, 1253 cm^{-1}

CI-MS (m/e): 487 (M^++1), 455, 423, 338, 191, 100

Example 41:

2-{1-[4-Benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)-3,5-difluoro-phenyl]-1*H*-[1,2,3]triazole-4-yl methyl}-isoindole-1,3-dione



The title compound was prepared from 4-(1-benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)-3,5-difluoro-phenylazide (3 grams, 9.2 mmol), obtained in preparation 28, following the same procedure as described for the preparation of 2-{1[4-Benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)-3-fluoro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl isoindole-1,3-dione in 67% yield (Example 33).

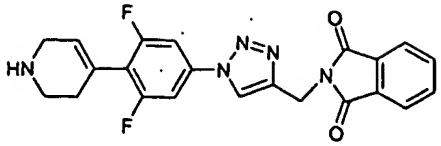
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.00 (s, 1H), 7.98-7.80 (m, 2H), 7.80-7.62 (m, 2H), 7.41-7.20 (m, 7H), 5.95-5.82 (m, 1H), 5.10 (s, 2H), 3.66 (s, 2H), 3.25-3.18 (m, 2H), 2.79-2.62 (m, 2H), 2.58-2.38 (m, 2H).

IR (KBr): 1721, 1429, 1397, 1026, 711 cm^{-1}

CI-MS (m/e): 522 (M+1), 418, 148

Example 42:

2-{1-[3,5-Difluoro-4-(1,2,3,6-tetrahydro-pyridin-4-yl)-phenyl]-1*H*-[1,2,3]triazol-4-yl methyl}-isoindole-1,3-dione



The title compound was prepared from 2-{1-[4-benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)- 3,5-difluoro-phenyl]-1*H*-[1,2,3]triazole-4-yl methyl}-isoindole-1,3-dione (2 grams, 3.9 mmol), obtained in example 41, following the same procedure as described for the preparation of 2-{1-[3-fluoro-4-(1,2,3,6-tetrahydro-pyridin-4-yl)-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl}-isoindole-1,3-dione (Example 34), in 60% yield.

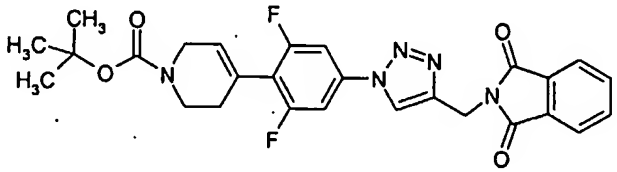
^{1}H NMR (DMSO-d_6, 200 MHz): δ 8.87 (s, 1H), 7.96-7.85 (m, 4H), 7.76 (d, J = 8.3 Hz, 2H), 7.62-7.48 (m, 1H), 5.99-5.84 (m, 1H), 4.93 (s, 2H), 3.50-3.32 (m, 2H), 3.04-2.84 (m, 2H), 2.36-2.18 (m, 2H)

IR (KBr): 3443, 2924, 1772, 171, 1632, 1509, 1455, 1432, 1397, 1288, 1033 cm^{-1}

CI-MS (m/e): 422 (M+1), 348

Example 43:

4-{4-[4-(1,3-Dioxo-1,3-dihydro-isoindole-2-ylmethyl)-[1,2,3]-triazol-1-yl]-2,6-difluoro-phenyl}-3,6-dihydro-2*H*-pyridin-1-carboxylic acid *tert*-butyl ester



To a solution of 2-{1-[3, 5-difluoro-4-(1, 2, 3, 6-tetrahydro-pyridin-4-yl)-phenyl]-1*H*-[1, 2, 3] triazol-4-ylmethyl}-isoindole-1,3-dione (150 mg, 0.356mmol), obtained in example 42, in dichloromethane (7 mL), added triethylamine (0.14 mL) followed by di-*tert*-butyldicarbonate (194 mg, 0.89 mmol) and allowed the reaction mixture to stir for 3 hours at 25-35 °C. Solvent was evaporated and the residue purified by column chromatography over silica gel (ethyl acetate/pet.ether, 3:2) to obtain the title compound as a light brown solid (100 mg, 54%).

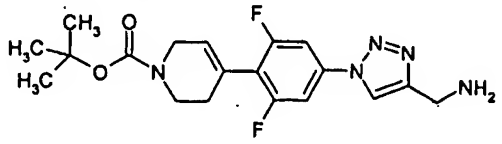
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.01 (s, 1H), 7.92-7.80 (m, 2H), 7.80-7.64 (m, 2H), 7.32 (d, J = 7.5 Hz, 2H), 5.96-5.84 (m, 1H), 5.08 (s, 2H), 4.16-4.03 (m, 2H), 3.64 (t, J = 5.4 Hz, 2H), 2.51-2.32 (m, 2H), 1.50 (s, 9H)

IR (KBr): 3460, 2926, 1720, 1428, 1366, 1238, 1179, 1044, 864, 714 cm^{-1}

CI-MS (m/e): 522 (M+1), 46, 422

Example 44:

4-[4-(4-Aminomethyl-[1,2,3] triazol-1-yl)-2,6-difluorophenyl]-3,6-dihydro-2*H*-pyridin-1-carboxylic acid *tert*-butyl ester



To 4-{4-[4-(1,3-dioxo-1,3-dihydro-isoindole-2-ylmethyl)-[1,2,3]triazol-1-yl]-2,6-difluoro-phenyl}-3,6-dihydro-2*H*-pyridin-1-carboxylic acid *tert*-butyl ester (100 mg, 0.192 mmol), obtained in example 43, in methanol (5 mL) was added hydrazine hydrate (0.08 mL) and refluxed the reaction mixture for 2 hours. Allowed the reaction mixture to cool and filtered over a celite pad, added silica gel (300 mg) to the filtrate, evaporated solvent and purified the residue by column chromatography (3% methanol/chloroform) to get the required product as a yellow solid (50 mg, 66%).

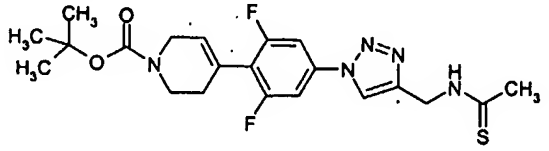
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.89 (s, 1H), 7.33 (d, J = 7.3 Hz, 2H), 5.94-5.83 (m, 1H), 4.16-3.98 (m, 4H), 3.69-3.58 (m, 2H), 2.49-2.36 (m, 2H), 1.26 (s, 9H).

IR (KBr): 3441, 2926, 1694, 1422, 1139, 1175, 1051, 863 cm^{-1}

CI-MS (m/e): 392 (M+1), 336

Example 45:

4-{2,6-Difluoro-4-[4-(thioacetylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-3,6-dihydro-2*H*-pyridin-1-carboxylic acid *tert*-butyl ester



To an ice cooled solution of 4-[4-(4-aminomethyl-[1,2,3]triazol-1-yl)-2,6-difluorophenyl]-3,6-dihydro-2*H*-pyridin-1-carboxylic acid *tert*-butyl ester (70 mg, 0.179 mmol), obtained in example 44, in THF (5 mL) was added triethylamine (0.06 mL, 0.448 mmol) followed by the addition of ethyl dithioacetate (0.05 mL, 0.447 mmol). The reaction mixture was brought to 25-35 °C and stirred for 12 hours. Evaporated the solvent on rotavapor and purified the residue by column chromatography over silica gel (ethyl

acetate/pet. ether 2:3) to afford the required compound as a pale yellow solid (57 mg, 71%).

Melting Point: 158-160 °C.

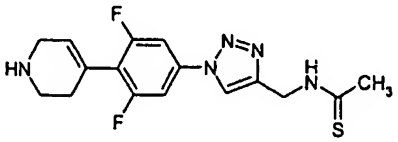
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.12 (s, 1H), 8.12-7.98 (m, 1H), 7.33 (d, J = 7.8 Hz, 2H), 5.98-5.84 (m, 1H), 5.02 (d, J = 5.4 Hz, 2H), 4.18-4.04 (m, 2H), 3.65 (t, J = 5.4 Hz, 2H), 2.62 (s, 3H), 2.52-2.36 (m, 2H),1.51 (s, 9H).

IR (KBr): 3434, 2926, 1695, 1426, 1172, 1050, 860, 538cm^{-1}

CI-MS (m/e): (M+1) 450, 394, 365

Example 46:

***N*-{1-[3,5-Difluoro-4-(1,2,3,6-tertrahydro-pyridin-4-yl)-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl}-thioacetamide**



A 60% solution of trifluoroacetic acid in dichloromethane (10 mL) was added to 4-{2,6-difluoro-4-[4-(thioacetylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}3,6-dihydro-2*H*-pyridin-1-carboxylic acid *tert*-butyl ester (100 mg, 0.22 mmol), obtained in example 45. The reaction mixture was allowed to stir at 25-35 °C for 3 hours. Toluene (15 mL) was added into the reaction mixture and evaporated to dryness on rotavapor. The residue was purified by column chromatography over silica gel (10% methanol-chloroform) to obtain the desired compound as a brown solid (52 mg, 66%).

Melting Point: 186-188 °C

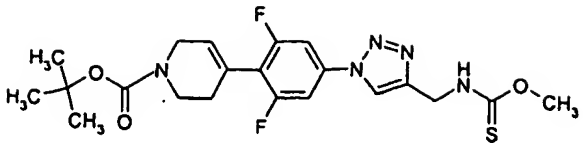
^{1}H NMR (DMSO-d_6): δ 10.62-10.42 (m, 1H), 9.22-8.98 (m, 2H), 8.86 (s, 1H), 7.88 (d, J = 8.5 Hz, 2H), 6.08 - 5.96 (m, 1H), 4.87 (d, J = 5.4 Hz, 2H), 3.90-3.72 (m, 2H), 3.42-3.24 (m, 2H), 2.68-2.45 (m, 2H), 2.42 (s, 3H).

IR (KBr): 3358, 2928, 1387, 1219, 1036, 761cm^{-1}

CI-MS (m/e): 350 (M+1)

Example 47:

4-{2,6-Difluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester



To a solution of 4-[4-(4-aminomethyl-[1,2,3]triazol-1-yl)-2,6-difluorophenyl]-3,6-dihydro-2*H*-pyridin-1-carboxylic acid *tert*-butyl ester (100 mg, 0.26 mmol), obtained in example 44, in THF (10 mL) was added triethylamine (0.07 mL) and brought the reaction temperature down to 0 °C. To this solution added carbon disulphide (0.02 mL, 0.31 mmol) and allowed the reaction mixture to stir at the same temperature for 4 hours, after which ethylchloroformate (0.02 mL, 0.26 mmol) was added and the reaction was continued for a further 1 hour at 0 °C . The solvent was removed on a rotavapor and the residue was dissolved in methanol (15 mL). The mixture was refluxed for 12 hours. Methanol was removed by evaporation and the residue was chromatographed over silica gel (25% ethyl acetate/pet.ether) to obtain the desired product as a creamy solid (61 mg, 52%).

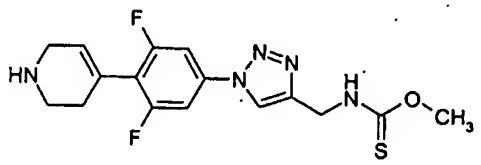
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.16 and 7.87(two s, 1H, in 3:1 ratio), 7.35 (d, J = 7.3Hz, 2H), 7.09-6.87 (m, 1H), 6.00-5.80 (m, 1H), 4.92 and 4.67 (two d, J = 5.9 Hz, 2H,in 3:1 ratio), 4.24-4.02 (m, 2H), 3.98 (s, 3H), 3.76-3.32 and 3.32-3.20 (two m, 2H in 6:1 ratio), 2.54-2.34 (m, 2H), 1.50 (s, 9H).

IR (KBr): 3442, 1692, 1515, 1423, 1239, 1161, 1116, 1015, 854 cm^{-1}

CI-MS (m/e): 466 (M+1), 434, 410, 378.

Example 48:

{1-[3,5-Difluoro-4-(1,2,3,6-tetrahydro-pyridin-4-yl)-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl}-thiocarbamic acid *O*-methyl ester:



A 60% solution of trifluoroacetic acid in dichloromethane (5 mL) was added to 4-{2,6-difluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (60 mg, 0.12 mmol), obtained in example 47, and allowed to stir at 25-35 °C for 3 hours. Toluene (15 mL) was added into the reaction mixture and evaporated to dryness under vacuum. The residue was purified

by column chromatography over silica gel (9%methanol-chloroform) to get a brown solid (45 mg, 95%)

Melting Point : 120-122 °C.

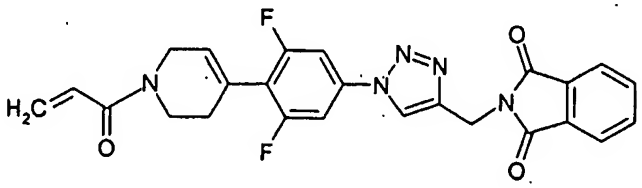
^{1}H NMR ($CDCl_3$+DMSO-d_6, 200 MHz): δ 9.20-9.02 (m, 1H), 8.39 and 8.30 (two s, 1H, rotamers in 3:1 ratio), 7.49 (d, J = 7.8 Hz, 2H), 5.98-5.88 (m, 1H), 4.85 (d, J = 5.4 Hz, 2H), 4.62-4.50 (m, 1H), 4.05-3.98 (two s, 3H, rotamers in 1:3 ratio), 3.80-3.68 (m, 2H), 3.34-3.16 (m, 2H), 2.64-2.44 (m, 2H)

IR (KBr): 3432, 1680, 1414, 1203 cm^{-1}

CI-MS (m/e): 366 (M+1), 334, 318

Example 49:

2-{1-[4-(1-Acrolyl-1,2,3,6-tetrahydro-pyridin-4-yl)-3,5-difluoro-phenyl}-1*H*-[1,2,3] triazole-4-yl} isoindole-1,3-dione



To an ice cooled solution of 2-{1-[3,5-difluoro-4-(1,2,3,6-tetrahydro-pyridin-4-yl)-phenyl]-1*H*-[1,2,3]triazol-4-yl methyl}-isoindole-1,3-dione (1.08 grams, 2.37 mmol), obtained in example 42, in dichloromethane (20 mL), was added triethylamine (0.5 mL) followed by acryloyl chloride (0.231 mL, 2.85 mmol) and then mixture was stirred at 25-35 °C for 12 hours. The reaction mixture was diluted with dichloromethane (40 mL) and washed with water followed by brine. Evaporation of the organic layer and purification of the resulting residue by flash chromatography (1% methanol-chloroform) yielded the desired compound (800 mg, 71%) as a white solid.

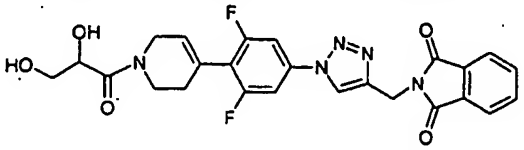
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.02 (s, 1H), 7.90-7.85 (m, 2H), 7.75-7.71 (m, 2H), 7.33 (d, J = 7.8 Hz, 2H), 6.70-6.56 (m, 1H), 6.55-6.22 (m, 1H), 6.00-5.80 (m, 1H), 5.79-5.62 (d, J = 11.7 Hz, 1H), 5.07 (s, 2H), 4.32-4.26 (m, 2H), 3.89-3.77 (m, 2H), 2.56-2.38 (m, 2H).

IR (KBr): 2925, 1721, 1642, 1434, 1045, 713 cm^{-1}

CI-MS (m/e): 476 (M+1)

Example 50:

2-(1-{4-[2,3-Dihydroxy-propionyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-isoindole-1,3-dione



The title compound was prepared from 2-{1-[4-(1-acryloyl-1,2,3,6-tetrahydro-pyridin-4-yl)-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazole-4-yl}isoindole-1,3-dione (500 mg, 1.05 mmol), obtained in example 49, following the same procedure as described for the preparation of 2-(1-{4-[4-(2,3-dihydroxy-propionyl)-piperzin-1-yl]-3-fluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-isoindole-1,3-dione (Example 15), in 56% yield.

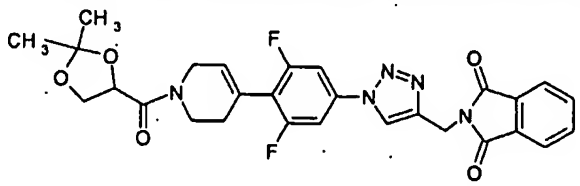
^{1}H NMR ($CDCl_3$+DMSO-d_6, 200 MHz): δ 8.47 (s, 1H), 7.90-7.64 (m, 4H), 7.52 (d, J = 8.0 Hz, 2H), 6.00-5.82 (m, 1H), 5.04 (s, 2H), 4.57-4.20 (m, 5H), 3.90-3.60 (m, 4H), 2.40-2.20 (m, 2H)

IR (KBr): 3423, 2926, 1716, 1631, 1396, 1047, 858 cm^{-1}

CI-MS (m/e): 510 (M^+), 480, 422.

Example 51:

2-(1-{4-[4,4-Dimethyl-[1,3]dioxolane-2-carbonyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-3,5-difluoro-phenyl}-1*H*-[1.2.3]triazol-4-ylmethyl)-isoindole-1,3-dione :



The title compound was prepared from 2-(1-{4-[1,2,3-dihydroxy-propionyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-isoindole-1,3-dione (500 mg, 0.98 mmol), obtained in example 50, following the same procedure as described for the preparation of 2-(1-{4-[4-(2,2-dimethyl-[1,3]dioxolane-4-carbonyl)-piperazin-1-yl]-3-fluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-isoindole-1,3-dione (Example 18), in 84% yield.

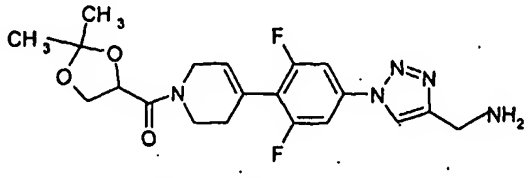
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.01 (s, 1H), 7.90-7.85 (m, 2H), 7.7.5-7.7.1 (m, 2H), 7.33 (d, J = 7.8 Hz, 2H), 5.99-5.82 (m,1H), 5.07 (s, 2H), 4.70 (t, J = 6.2 Hz, 1H), 4.60-4.22 (m, 2H), 4.22-3.84 (m, 3H), 3.82-3.60 (m, 1H), 2.60-2.38 (m, 2H), 1.42 (s, 6H)

IR (KBr): 1719, 1633, 1454, 1396, 1045, 859, 758 cm^{-1}

CI-MS (m/e): 550 (M^+), 377, 148

Example 52:

{4-[4-(4-Aminomethyl-[1,2,3]triazol-1-yl)-2,6-difluoro-phenyl]-3,6-dihydro-2*H*-pyridin-1-yl}-(4,4-dimethyl-[1,3]dioxolane-2-yl)-methanone



The title compound was prepared from 2-(1-{4-[4,4-dimethyl-[1,3]dioxolane-2-carbonyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-3,5-difluoro-phenyl}-1*H*-[1.2.3]triazol-4-ylmethyl)-isoindole-1,3-dione (320 mg, 0.58 mmol), obtained in example 51, following the same procedure as described for the preparation of {4-[4-(4-aminomethyl-[1,2,3]triazol-1-yl)-2-fluoro-phenyl]-piperazin-1-yl}-(2,2-dimethyl-[1,3]dioxolan-4-yl)methanone (Example 19).

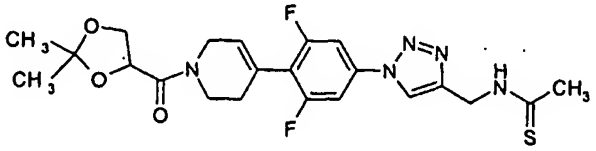
^{1}H NMR ($CDCl_3$+ DMSO-d_6, 200 MHz): δ 8.40 (s, 1H), 7.50 (d, J = 7.8 Hz, 2H), 5.99-5.86 (m, 1H), 4.90-4.78 (m, 1H), 4.50-4.20 (m, 3H), 4.20-4.06 (m, 2H), 4.05-3.84 (m, 2H), 3.84-3.67 (m, 1H), 2.50 (m, 2H), 1.40 (s, 6H)

IR (KBr): 3433, 2924, 1635, 1450, 1235, 1027, 858 cm^{-1}

CI-MS (m/e): 420 (M^+), 163

Example 53:

***N*-(1-{4-[1-(2,2-Dimethyl-[1,3]dioxolane-4-carbonyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thioacetamide**



To an ice cooled solution of{4-[4-(4-aminomethyl-[1,2,3]triazol-1-yl)-2,6-difluoro-phenyl]-3,6-dihydro-2*H*-pyridin-1-yl}-(4,4-dimethyl-[1,3]dioxolane-2-yl)-methanone (120 mg, 0.285 mmol), obtained in example 52, in THF (15 mL) was added triethylamine (0.59 mL, 0.516 mmol) and ethyl dithioacetate (0.36 mL, 0.314 mmol). The reaction was left to stir at 25-35 °C for 12 hours. Solvent was removed under reduced

pressure and the residue was purified by chromatography over silica gel (60% ethyl acetate/pet.ether) to get the title compound as a white solid (50 mg, 37%).

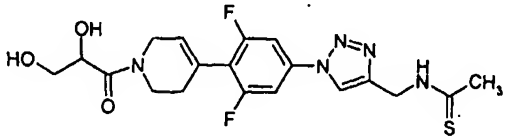
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.38-8.21 (m, 1H), 8.16 (s, 1H), 7.35 (d, J = 7.8 Hz, 2H), 5.96-5.82 (m, 1H), 5.00 (d, J = 5.4Hz, 2H), 4.75 (t, J = 6.3 Hz, 1H), 4.60-4.27 (m, 2H), 4.22-4.08 (m, 2H), 4.08-3.91 (m, 1H), 3.90-3.60 (m, 1H), 2.60 (s, 3H), 2.60-2.30 (m, 2H), 1.43 (s, 6H)

IR (KBr): 3440, 1633, 1453, 1043, 858 cm^{-1}

CI-MS (m/e): 478 (M+1), 405, 350, 294, 228

Example 54:

***N*-(1-{4-[1-(2,3-Dihydroxy-propionyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thioacetamide :**



To a solution of *N*-(1-{4-[1-(2,2-dimethyl-[1,3]dioxolane-4-carbonyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thioacetamide (180 mg, 0.376 mmol), obtained in example 53, in THF (8 mL) and added 1N HCl (2 mL). And mixture was allowed to stand at 25-35 °C for 6 days. Evaporated the solvent on a rotavapour and purified the residue by column chromatography over silica gel (methanol/chloroform, 0.03: 1) to obtain the desired product as a white solid (80 mg, 49%)

Melting Point : 158 °C.

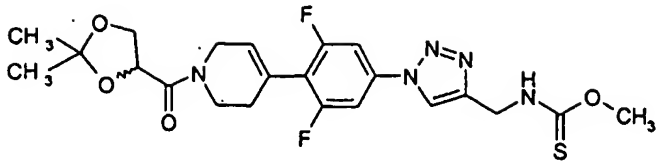
^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.54-10.44 (m, 1H), 8.88 (s, 1H), 7.85 (d, J = 8.4 Hz, 2H), 6.01-5.98 (m, 1H), 5.08-4.99 (m, 1H), 4.84 (d, J = 5.4 Hz, 2H), 4.78-4.70 (m, 1H), 4.45-4.20 (m, 2H), 4.20-4.16 (m, 1H), 3.95-3.63 (m, 2H), 3.62-3.50 (m, 1H), 3.50-3.40 (m, 1H), 2.50-2.30 (m, 2H), 2.49 (s, 3H)

IR (KBr): 3421, 1756, 1638, 1241, 1055, 1025 cm^{-1}

CI-MS (m/e): 438 (M+1), 420, 260

Example 55:

(1-{4-[1-(2,2-Dimethyl-[1,3]dioxolane-4-carbonyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester



To a solution of{4-[4-(4-aminomethyl-[1,2,3]triazol-1-yl)-2,6-difluoro-phenyl]-3,6-dihydro-2*H*-pyridin-1-yl}-(4,4-dimethyl-[1,3]dioxolane-2-yl)-methanone (300 mg, 0.72 mmol), obtained in example 52, in THF (15 mL) was added triethylamine (0.19 mL, 1.43 mmol) and brought the reaction temperature down to 0 °C . To this solution added carbon disulphide (0.052 mL, 0.86 mmol) and allowed the reaction mixture to stir at the same temperature for 4 hours, after which methylchloroformate (0.06 mL, 0.72 mmol) was added and the reaction was continued for another 1 hour at 0 °C The solvent was removed on a rotavapor. Methanol (15 mL) was added to the residue and the mixture was refluxed for 12 hours. Methanol was removed by evaporation and the residue was chromatographed over silica gel (ethyl acetate/pet.ether, 7:3) to obtain the desired product as a cream color solid (256 mg, 73%).

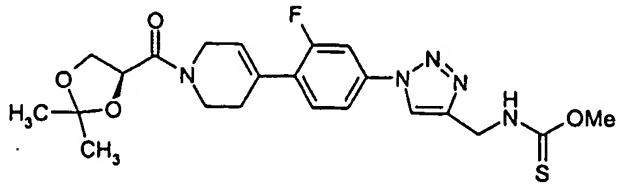
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.07 (s, 1H), 7.32 (d, *J* =7.8 Hz, 2H), 6.89-6.76 (m, 1H), 5.96-5.83 (m, 1H), 4.89 (d, *J* = 5.9 Hz, 2H), 4.70 (t, *J* = 6.3 Hz, 2H), 4.56-4.40 (m, 1H), 4.40-4.24 (m, 1H), 4.24-4.04 (m, 2H), 3.97 (s, 3H), 3.84-3.58 (m, 1H), 2,50-2.37 (m, 2H), 1.53 (s, 3H), 1.34 (s, 3H)

IR (KBr): 2926, 1634, 1512, 1454, 1203, 3413, 858 cm^{-1}

CI-MS (m/e): 494 (M+1), 462

Example 56:

{4-[1-((4S)2-2-Dimethyl-[1, 3] dioxolane-4-carbonyl)-1, 2, 3, 6-tetrahydro-pyridin-4-yl)-3-flouro-phenyl}-1H-[1, 2, 3] triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



N, N-Disopropylamine (0.05 mL, 0.289 mmol.), prop-2-ynyl-thiocarbamic acid-O-methyl ester (100 mg, 0.210 mmol), obtained in preparation 1, and copper iodide (28 mg, 0 .144 mmol) were added to a solution of [4-(4-Azido-2-fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-((4S)-2,2-dimethyl-[1,3] dioxolan-4-yl)-methanone (100 mg, 0.289 mmol.),

obtained in preparation 30, in DMF (5 mL) and stirred at 25-35 °C for 2 hours. The solvent was removed partially under reduced pressure. The residual solvent was diluted with ethyl acetate (5 mL) and washed with water followed by brine. The organic layer was dried over anhydrous sodium sulphate and evaporated under vacuum. The residue was purified by column chromatography (0.1:1 methanol/chloroform) to give the title product (250 mg, 44%).

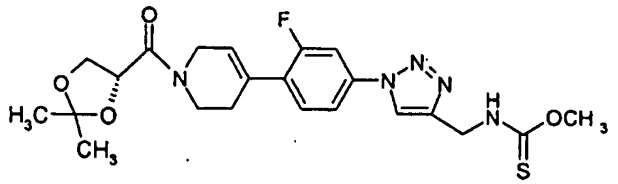
^{1}H NMR ($CDCl_3$, 200MHz): δ 8.00 and 7.92 (2s, 1H, rotamers in 3:1 ratio), 7.59-7.342 (m, 2H), 7.12-6.98 (m, 1H), 6.12-6.00 (m, 1H), 4.92 (d, J=5.8Hz, 2H), 4.80-4.60 (m, 1H), 4.56-4.26 (m, 2H), 4.26-2.08 (m, 2H), 4.08-3.90 (m, 4H), 3.80-3.60 (m, 1H), 2.72-2.42 (m, 2H), 1.43 (s, 6H)

IR (KBr): 3250, 2937, 1639, 1453, 1370, 1207, 1152, 1046, 871, 757 cm^{-1}

CI-MS (m/e): 476(M+1), 444 $(M-31)^+$

Example 57:

{4-[1-((4R)-2-2-Dimethyl-[1, 3] dioxolane-4-carbonyl)-1, 2, 3, 6-tetrahydro-pyridin-4-yl)-3-flouro-phenyl}-1H-[1, 2, 3] triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



Using the same procedure as described for the preparation of {4-[1-((4S)2-2-Dimethyl-[1, 3] dioxolane-4-carbonyl)-1, 2, 3, 6-tetrahydro-pyridin-4-yl)-3-flouro-phenyl}-1H-[1, 2, 3] triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester, obtained in example 56, the title product (250 mg, 73%) was obtained as a white solid (250 mg, 44%) from [4-(4-azido-2-fluoro-phenyl)-3,6-dihydro-2H--pyridin-1-yl]-((4R)-2,2-dimethyl-[1,3]dioxolan-4-yl)-methanone (250 mg, 0.723 mmol), obtained in preparation 31.

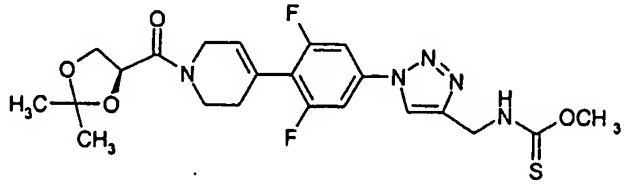
^{1}H NMR ($CDCl_3$, 400MHz): δ 8.13 and 8.00 (2s, 1H, rotamers in 4:1 ratio), 7.59-7.48 (m, 2H), 7.39 (t, J=7.8Hz, 1H), 6.93-6.85 (m, 1H), 6.10-6.02 (m, 1H), 4.92 & 4.66 (two d, 2H, rotamers in the ratio 3:1), 4.73 (dd, J_1=6.3Hz, J_2=13.3Hz, 1H), 4.55-4.45 (m, 1H), 4.45-4.27 (m, 1H), 4.20-4.10 (m, 2H), 4.00 (s, 3H), 4.12-3.92 (m, 2H), 3.80-3.67 (m, 1H), 2.60-2.48 (m, 2H), 1.48 (s, 6H)

IR (Neat): 3248, 1639, 1452, 1207, 1048, 871 cm^{-1}

CI-MS (m/e): 476 (M+1), 444 $(M-31)^+$

Example 58:

(1-{4[1-((4S)-2-2-Dimethyl-[1, 3] dioxolane-4-carbonyl)-1, 2, 3, 6-tetrahydro-pyridin-4-yl)-3, 5-diflouro-phenyl}-1H-[1, 2, 3] triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



Using the same procedure as described for the preparation of {4-[1-((4R)-2-2-Dimethyl-[1, 3] dioxolane-4-carbonyl)-1, 2, 3, 6-tetrahydro-pyridin-4-yl)-3-flouro-phenyl}-1H-[1, 2, 3] triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester (Example 57), the title compound (250 mg) was obtained from [4-(4-azido-2, 6-difluoro-phenyl)-3, 6-dihydro-2H-pyridin-1-yl]-((4S)-2, 2-dimethyl-[1, 3] dioxolan-4-yl)-methanone (420 mg), obtained in preparation 32.

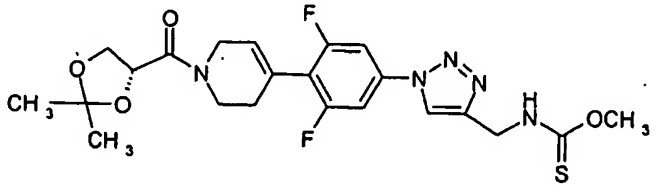
^{1}H NMR ($CDCl_3$, 200MHz): δ 8.12 and 7.88 (2s, 1H, rotamers in 3:1 ratio), 7.36(d, J=7.8 Hz, 2H), 7.05-6.88 (m, 1H), 6.06-5.88 (m,1H), 4.92-4.68 (two d, J=5.8 Hz, 2H, rotamers in the ratio 3:1), 4.75 (t, J=6.3 Hz, 1H), 4.60-4.48 (m, 1H), 4.48-4.30 (m, 1H), 4.30-4.17 (m, 2H), 4.12 & 4.00 (two s, 3H, rotamers in the ratio 1:3), 4.10-3.92 (m, 1H), 3.85-3.62 (m, 1H), 2.80-2.38 (m, 2H), 1.43 (s, 6H)

IR (KBr): 3378, 3139, 2361, 1636, 1455, 1283, 1074, 987, 857 cm^{-1}

CI-MS (m/e): 494 (M+1), 462 $(M-31)^+$

Example-59:

(1-{4[1-((4R)-2-2-Dimethyl-[1, 3] dioxolane-4-carbonyl)-1, 2, 3, 6-tetrahydro-pyridin-4-yl)-3, 5-diflouro-phenyl}-1H-[1, 2, 3] triazol-4-yl-methyl)-thiocarbamic acid O-methyl ester



Using the same procedure as described for the preparation of {4-[1-((4S)2-2-Dimethyl-[1, 3] dioxolane-4-carbonyl)-1, 2, 3, 6-tetrahydro-pyridin-4-yl)-3-flouro-

phenyl}-1H-[1, 2, 3] triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester (Example 56), the title compound (460 mg) was synthesized from [4-(4-azido-2, 6-difluoro-phenyl)-3, 6-dihydro-2H-pyridin-1-yl]-((4R)-2, 2-dimethyl-[1,3] dioxolan-4-yl)-methanone, which is obtained in preparation 33.

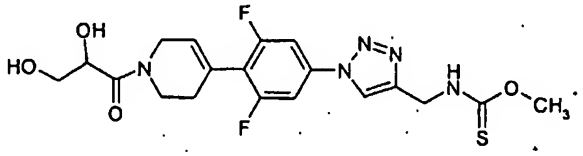
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.02 and 7.87(two s, rotamers in the ratio 3:1, 1H), 7.38 (d, J= 7.3 Hz, 2H), 7.01-6.92 (m, 1H), 6.01-5.90(m, 1H), 4.92 & 4.68(two d, J=6.3Hz, rotamers in the ratio 3:1, 2H), 4.74(t, J=6.3Hz, 1H), 4.30-4.17(m, 2H), 4.12 & 4.00(two s, rotamers in the ratio 1:3, 3H), 4.10-3.92(m, 1H), 3.85(m, 1H), 2.75-2.35(m, 2H), 1.43(s, 6H).

IR (Neat): 3257, 2923, 1633, 1512, 1453, 1205, 1148, 1047, 987 cm^{-1}

CI-MS (m/e): 494 (M+1)

Example 60:

(1-{4-[1-(2,3-Dihydroxy-propionyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester



To a solution of (1-{4-[1-(2,2-dimethyl-[1,3]dioxolane-4-carbonyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester (256 mg, 0.52 mmol), obtained in example 55, in THF (8 mL) added 1N HCl (3 mL) and reaction mixture was allowed to stand at 25-35 °C for 6 days. Evaporated the solvent on a rotavapour and purified the residue by column chromatography over silica gel (methanol/chloroform, 0.04: 1) to furnish the desired product as a white solid (180 mg, 77%)

Melting Point: 132-134 °C.

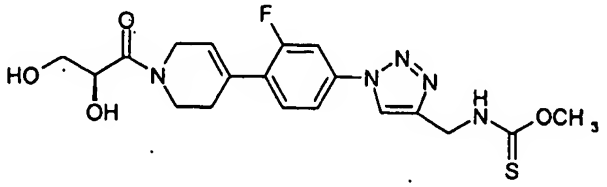
^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.04-8.98 and 8.98-8.88 (two m, 1H in 1:2 ratio), 8.35 and 8.25 (two s, 1H in 4:1 ratio), 7.48 (d, J = 7.8 Hz, 2H), 5.98-5.88 (m, 1H), 4.86 and 4.60 (two d, J = 5.9 Hz, 2H in 4:1 ratio), 4.56-4.45 (m, 1H), 4.42-4.32 (m, 1H), 4.32-4.18 (m, 2H), 4.07 and 3.98 (two s, 3H, rotamers in1: 4 ratio), 3.84-3.66 (m, 5H), 2.58-2.48 (m, 2H)

IR (KBr): 3428, 2927, 1637, cm^{-1}

CI-MS (m/e): 454(M+1), 422, 380

Example 61:

(1-{4-[1-(2(S), 3-Dihydroxy-propionyl)-1, 2, 3, 6-tetrahydro-pyridin-4-yl]-3-fluoro-phenyl}-1H-[1, 2, 3] triazol-4-ylmethyl)-thiocarbamic acid 0-methyl ester



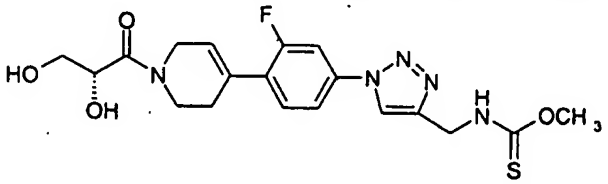
To a solution of {4-[1-((4S)-2-2-Dimethyl-[1, 3] dioxolane-4-carbonyl)-1,2,3,6-tetrahydro-pyridin-4-yl)-3-flouro-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester (200 mg, 0.42 mmol.), obtained in example 56, was added 2N HCl (5 mL). The reaction mixture was kept at 25-35 °C for 48 hours. The solvent was removed under reduced pressure and the crude residual product was purified by column chromatography (0.1:1 methanol: chloroform) to get the product as a brown solid (130 mg, 71%).

^{1}H NMR ($CDCl_3$, 200MHz): δ 9.25-9.10 (m, 1H), 8.36& 8.27 (s, 1H, rotamers in the ratio 3:1), 7.69-7.50 (m, 2H), 7.48-7.38 (m, 1H), 6.18-6.03 (m, 1H), 4.84 & 4.57 (two d, 2H, rotamers in the ratio 3:1), 4.54-4.32 (m, 3H), 4.34-4.21 (m, 2H), 4.04 & 3.96 (two s, 3H, rotamers in the ratio 3:1), 3.83-3.60(m, 4H), 2.72-2.50 (m, 2H)

IR (KBr): 3423, 2926, 210, 1623, 1541, 1541, 1438, 1231, 1044, 867, 812 cm^{-1}

Example 62:

1-{4-[1-(2(R), 3-Dihydroxy-propionyl)-1, 2, 3, 6-tetrahydro-pyridin-4-yl]-3-fluoro-phenyl}-1H-[1, 2, 3] triazol-4-ylmethyl)-thiocarbamic acid 0-methyl ester



{4-[1-((4R)-2-2-Dimethyl-[1, 3] dioxolane-4-carbonyl)-1, 2, 3, 6-tetrahydro-pyridin-4-yl)-3-flouro-phenyl}-1H-[1, 2, 3] triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester (250 mg, 0.526 mmol.), obtained in example 57, was reacted using the same procedure as described for the preparation of (1-{4-[1-(2(S), 3-dihydroxy-propionyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-3-fluoro-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic

acid 0-methyl ester (Example 61), to yield the desired product (140 mg, 61%) as a brown solid (140 mg, 61%)

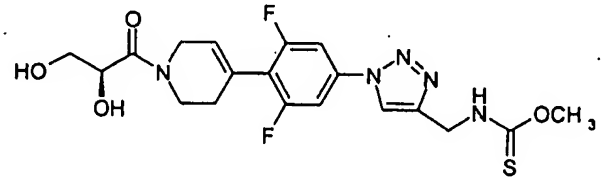
^{1}H NMR ($CDCl_3$, 200MHz): δ 8.33 and 8.22 (2s, 1H, rotamers in 3:1 ratio), 7.69-7.50 (m, 2H), 7.48-7.38 (m, 1H), 6.18-5.98 (m, 1H), 4.85 & 4.57 (two d, 2H, rotamers in the ratio 3:1), 4.54-4.32 (m, 3H), 4.32-4.25 (m, 2H), 4.01 & 3.97 (two s, 3H, rotamers in the ratio 1:3), 3.80-3.58 (m, 4H), 2.72-2.49 (m, 3H).

IR (KBr): 3424, 2925, 1626, 1402, 1324, 1198, 1046, 867, 695cm^{-1}

CI-MS (m/e): 404 $(M-31)^{+\cdot}$

Example 63:

(1-{4-[1-(2(S), 3-Dihydroxy-propionyl)-1, 2, 3, 6-tetrahydro-pyridin-4-yl]-3,5-difluoro-phenyl}-1H-[1, 2, 3] triazol-4-ylmethyl)-thiocarbamic acid 0-methyl ester



Using the same procedure as described for the preparation of (1-{4-[1-(2(S), 3-dihydroxy-propionyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-3-fluoro-phenyl}-1H-[1,2,3] triazol-4-ylmethyl)-thiocarbamic acid 0-methyl ester (Example 61), the title compound was synthesized from (1-{4[1-((4S)-2-2-Dimethyl-[1, 3] dioxolane-4-carbonyl)-1, 2, 3, 6-tetrahydro-pyridin-4-yl)-3,5-diflouro-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester, obtained in example 58.

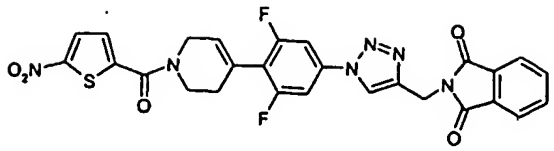
^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.58-9.35 (m, 1H), 8.63 and 8.60 (2s, 1H, rotamers in 4:1 ratio), 7.65 (d, J=7.8Hz, 2H), 6.05-5.85 (m, 1H), 4.79 (d,J=5.8Hz, 2H), 4.70-4.55 (m, 1H), 4.55-4.22 (m, 2H), 4.39-4.19 (m, 2H), 4.01& 3.94 (two s, 3H, rotamers in the ratio 1:3), 3.90-3.75 (m, 1H), 3.75-3.55 (m, 2H), 2.61-2.39 (m, 2H).

IR (Neat): 3268, 2945, 1630, 1453, 1202, 1049, 859 cm^{-1}

CI-MS (m/e): 454 (M+1), 422 $(M-31)^+$

Example 64:

2-(1-{3,5-Difluoro-4-[1-(5-nitro-thiophene-2-carbonyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-isoindole-1,3-dione



A solution of 5-nitro-thiophene-2-carboxylic acid (600 mg, 4.26 mmol) in thionyl-chloride (15 mL) was refuxed for 1 hour. Evaporated thionyl chloride on rotavapor and dried the residue under high vacuum. To a solution of the residue in dry THF (20 mL) added triethylamine (0.29 mL, 2.1 mmol) and a solution of 2-{1-[3,5-difluoro-4-(1,2,3,6-tetrahydro-pyridin-4-yl)-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl}-isoindole-1,3-dione, (600 mg, 1.425 mmol), obtained in example 42, in dry THF (20 mL) under nitrogen atmosphere at 0 °C and left the reaction mixture to stir at 25-35 °C for 12 hours. Diluted the reaction mixture with dichloromethane (30 mL) and washed with water followed by brine. Evaporated the organic solvent on a rotavapor and purified the residue over silica gel by column chromatography (1% methanol/chloroform) to obtain the title compound as a brown solid (659 mg, 80%)

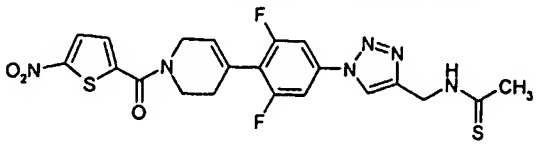
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 (s, 1H), 7.90-7.85 (m, 3H), 7.76-7.7 (m, 2H), 7.36(d, *J* = 7.9 Hz, 2H), 7.25 (d, *J* = 4.3 Hz, 1H), 6.00-5.96 (m, 1H), 5.08 (s, 2H), 4.41-3.97 (m, 2H), 3.97-3.86 (m, 2H), 2.63-2.57 (m, 2H)

IR (KBr): 3422, 2926, 1721, 1625, 1529, 1241, 768 cm^{-1}

ES-MS (m/e): 577 (M+1), 301, 255

Example 65:

***N*-(1-{3, 5-Difluoro-4-[1-(5-nitro-thiophene-2-carbonyl)-1, 2, 3, 6-tetrahydro-pyridin-4-yl]-phenyl}-1*H*-[1, 2, 3] triazol-4-ylmethyl)-thioacetamide**



The title compound was prepared from 2-(1-{3,5-difluoro-4-[1-(5-nitro-thiophene-2-carbonyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-isoindole-1,3-dione (659 mg, 1.14 mmol), obtained in example 64, following the same procedure as described for the preparation of *N*-(1-{3-fluoro-4-[1-(5-nitro-furan-2-carbonyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thioacetamide (Example 39), in 41% yield..

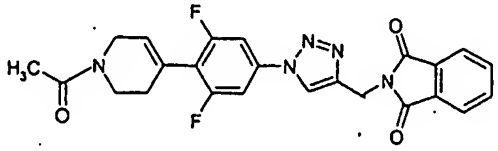
^{1}H NMR (CD_3OD, 200 MHz): δ 8.59 (s, 1H), 7.98 (d, J = 4.0 Hz, 1H), 7.62 (d, J = 7.5 Hz, 2H), 7.47 (d, J = 4.0 Hz, 1H), 6.06-5.94(m, 1H), 4.98-4.92 (m, 2H), 4.48-4.36 (m, 2H), 4.02-3.92 (m, 2H), 2.68-2.52 (m, 2H), 2.50 (s, 3H)

IR (KBr): 3440, 1630, 1338, 1048, 640 cm^{-1}

ES-MS (m/e): 505 (M+1)

Example 66:

2-{1-[4-(1-Acetyl-1,2,3,6-tetrahydro-pyridin-4-yl)-3,5-difluoro-phenyl]-1*H*-[1,2,3] triazol-4-ylmethyl)-isoindole-1,3-dione



To an ice cooled solution of 2-{1-[3,5-difluoro-4-(1,2,3,6-tetrahydro-pyridin-4-yl)-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl}-isoindole-1,3-dione (100 mg, 0.237 mmol), obtained in example 42, in dichloromethane (10 mL) was added triethylamine (0.008 mL) followed by acetyl chloride (0.02 mL, 0.285 mmol). The reaction mixture was left to stir for 12 hours at 25-35 °C. To the reaction mixture added dichloromethane (20 mL) and washed with water followed by brine. Removed the solvent on rotavapor and chromatographed the residue over silica gel (2.5% methanol/chloroform) to obtain the required product as a white solid (80 mg, 73%).

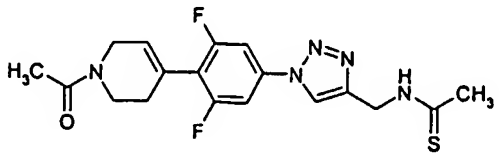
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.01 (s, 1H), 7.90-7.80 (m, 2H), 7.80-7.62 (m, 2H), 7.30 (d, J = 7.3 Hz, 2H), 5.99-5.81 (m, 1H), 5.06 (s, 2H), 4.30-4.10 (m, 2H), 3.81 (t, J = 5.4 Hz, 1H), 3.65 (t, J = 5.4 Hz, 1H), 2.58-2.40 (m, 2H), 2.14 (s, 3H)

IR (KBr): 3433, 1711, 1632, 1428, 1040, 856 cm^{-1}

CI-MS (m/e):(M+1) 464

Example 67:

***N*-{1-[4-(1-acetyl-1,2,3,6-tetrahydro-pyridin-4-yl)-3,5-difluoro-phenyl]-1*H*-[1,2,3] triazol-4-ylmethyl)-thioacetamide**



The title compound was prepared from 2-{1-[4-(1-acetyl-1,2,3,6-tetrahydro-pyridin-4-yl)-3,5-difluoro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl)-isoindole-1,3-dione (450 mg, 0.97 mmol), obtained in example 66, following the same procedure as described for the preparation of *N*-{1-[4-(1-acetyl-1,2,3,6-tetrahydro-pyridin-4-yl)-3-fluoro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl}-thioacetamide in 50% yield.

Melting Point: 182 °C.

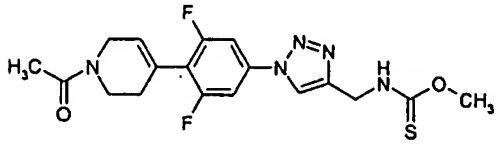
^{1}H NMR ($CDCl_3$+DMSO-d_6, 200 MHz): δ 10.22-10.11 (m, 1H), 8.44 (s, 1H), 7.50 (d, *J* = 7.8 Hz, 2H), 6.01-5.89 (m, 1H), 4.95 (d, *J* =5.4 Hz, 2H), 4.30-4.19(m, 2H), 3.81(t, *J* = 5.4 Hz, 1H), 3.71 (t, *J* = 5.4 Hz, 1H), 2.62-2.40 (m, 2H), 2.54 (s, 3H), 2.20 (s, 1H)

IR (KBr): 3437, 1615, 1451, 1035, 846 cm^{-1}

CI-MS (m/e): 392 (M+1), 363, 289

Example 68:

{1-[4-(1-Acetyl-1,2,3,6-tetrahydro-pyridin-4-yl)-3,5-difluoro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester



To an ice cooled solution of 1-{4-[4-(4-aminomethyl-[1,2,3]triazol-1-yl)-2,6-difluoro-phenyl]-3,6-dihydro-2*H*-pyridin-1-yl}-ethanone (200 mg, 0.60 mmol), in THF (10 mL) was added triethylamine (0.1 mL) followed by carbon disulphide (0.04 mL, 0.72 mmol) and allowed the reaction mixture to stir at the same temperature for 4 hours, after which ethylchloroformate (0.05 mL, 0.54 mmol) was added and the reaction was continued for another 1 hour at 0 °C. The solvent was removed under reduced pressure, methanol (15 mL) was added to the residue and the reaction mixture was refluxed for 12 hours. Methanol was removed by evaporation and the residue was chromatographed over silica gel (1% methanol/chloroform) to obtain the desired product as a white solid (68 mg, 28%).

Melting Point: 174 °C.

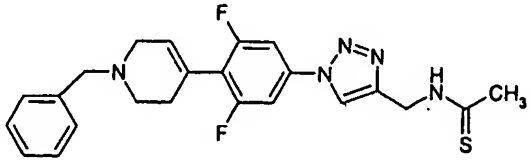
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.12 and 7.88 (two s, 1H, rotamers in 4:1 ratio), 7.35 (d, *J* = 7.5 Hz, 2H), 7.08-6.90 (m, 1H), 6.00-6.82 (m, 1H), 4.91 and 4.70 (d, *J* = 5.9 Hz, 2H, rotamers in 4:1 ratio), 4.35-4.20 (m, 1H), 4.20-4.05 (m, 1H), 4.10 and 4.00 (two s, 3H, rotamers in 1:4 ratio), 383 (t, *J* = 5.4 Hz, 1H), 3.68 (t, *J* = 5.4 Hz, 1H), 2.50-2.40 (m, 2H), 2.18 (s, 3H)

IR (KBr): 3420, 2925, 1633, 1453, 1273, 1053

CI-MS (m/e): 408 (M+1), 376

Example 69:

***N*-{1-[4-(1-Benzyl-1, 2, 3, 6-tetrahydro-pyridin-4-yl)-3, 5-difluro-phenyl]-1*H*-[1,2,3] triazol-4-ylmethyl}-thioacetamide**



To a solution of 2-{1-[4-benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)-3,5-difluoro-phenyl]-1*H*-[1,2,3]triazole-4-ylmethyl isoindole-1,3-dione (500 mg, 0.97 mmol), obtained in example 41, in methanol (10 mL) was added hydrazinehydrate (0.42 mL) and refluxed the reaction mixture for 2 hours. The reaction mixture was allowed to stir for 6 hours at ambient temperature. Filtered the reaction mixture over a celite pad and the filtrates were concentrated. The residue was chromatographed over silica gel (9% methanol/chloroform) to obtain {1-[4-(1-benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)-3,5-difluoro-phenyl]-1*H*-[1,2,3]triazol-4-yl}methylamine as a creamy solid (370 mg). To an ice cooled solution of this amine (100 mg, 0.263 mmol) in dry THF (3 mL) was added triethylamine (0.09 mL), followed by ethyl dithioacetate (0.08 mL, 0.657 mmol) and allowed the reaction mixture to warm up to 25-35 °C and stirred for 12 hours. The reaction mixture was concentrated under vacuum and the residue purified by column chromatography over silica gel (40% ethyl acetate/pet.ether) to furnish the desired compound as a white solid (80 mg, 70%).

Melting Point: 140-142 °C.

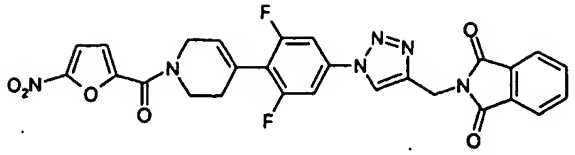
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.29-8.04 (m, 1H), 8.11 (s, 1H), 7.46-7.16 (m, 7H), 5.96-5.84 (m, 1H), 5.01 (d, J = 5.4 Hz, 2H), 3.68 (s, 2H), 3.28-3.18 (m, 2H), 2.82-2.63 (m, 2H), 2.62 (s, 3H), 2.48-2.38 (m, 2H)

IR (KBr): 3220, 1631, 1454, 1218, 1043, 757, 700, cm^{-1}

CI-MS (m/e): 440 (M+1)

Example 70:

2-(1-[3.5-Difluoro-4-[1-(5-nitro-furan-2-carbonyl)-1, 2, 3, 6-tetrahydro-pyridin-4-yl]-phenyl}-1*H*-[1, 2, 3] triazol-4-ylmethyl)-isoindole-1, 3-dione



To a solution of 2-{1-[3,5-difluoro-4-(1,2,3,6-tetrahydro-pyridin-4-yl)-phenyl]-1*H*-[1,2,3]triazol-4-yl methyl}-isoindole-1,3-dione (420 mg, 0.99 mmol), obtained in example 42, in dry dichloromethane (15 mL) was added triethylamine (0.413 mL, 2.97 mmol) and cooled the reaction mixture to 0 °C . At this temperature, added 2-nitro-5-furoyl chloride (210 mg, 1.19 mmol) to the reaction mixture and stirred at 25-35 °C for 12 hours. The reaction mixture was diluted with dichloromethane (50 mL) washed with water followed by brine and then dried over sodium sulphate. The volatiles were removed under reduced pressure and the residue was purified by column chromatography over silica gel (40% ethyl acetate/pet.ether) to get the title compound as a pale yellow solid (410 mg, 73%)

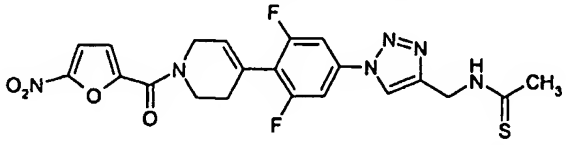
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.02 (s, 1H), 7.88-7.82 (m, 2H), 7.82-7.70 (m, 2H), 7.40-7.20 (m, 4H), 6.02-5.84 (m, 2H), 5.06 (s, 2H), 4.62-4.42(m, 1H), 4.42-4.30 (m, 1H), 4.12-3.90 (m, 2H), 2.70-2.50 (m, 2H)

IR (KBr): 1720, 1630, 1432, 1355, 1039, 713 cm^{-1}

ES-MS (m/e): 561 (M+1)

Example 71:

***N*-(1-[3.5-Difluoro-4-[1-(5-nitro-furan-2-carbonyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-phenyl}-1*H*-[1, 2, 3] triazol-4-ylmethyl)-thioacetamide**



The title compound was prepared from 2-(1-[3.5-difluoro-4-[1-(5-nitro-furan-2-carbonyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-isoindole-1,3-dione (410 mg, 0.732 mmol), obtained in example 70, following the same procedure as descibed for the prepration of *N*-(1-{3-fluoro-4-[1-(5-nitro-furan-2-carbonyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thioacetamide (Example 39) in 48% yield.

Melting Point: 193 °C .

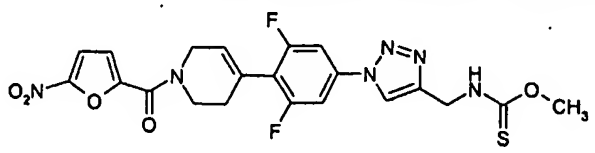
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.32 –8.21 (m, 1H), 8.19 (s, 1H), 7.39-7.36 (m, 3H), 7.30-7.22 (merged with $CDCl_3$ peak, 1H), 6.02-5.98 (m,1H), 5.05 (d, J = 5.4 Hz, 2H), 4.70-4.58 (m, 1H), 4.50-4.40 (m, 1H), 4.10-3.90 (m, 2H), 2.70-2.60 (m, 2H), 2.60(s, 3H)

IR (KBr): 1630, 1529, 1437, 1355, 1037, 846 cm^{-1}

CI-MS (m/e): 489 (M+1), 457, 350

Example 72:

1-{3.5-Difluoro-4-[1-(5-nitro-furan-2-carbonyl)-1, 2, 3, 6-tetrahydro-pyridin-4-yl]-phenyl}-1*H*-[1, 2, 3] triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester



To an ice cooled solution of {4-[4-(4-aminomethyl-[1,2,3]triazol-1-yl)-2,6-difluoro-phenyl]-3,6-dihydro-2*H*-pyridin-1-yl}-(5-nitro-furan-2-yl)-methanone (150 mg, 0.345 mmol) in dry THF (10 mL), was added triethylamine (0.058 mL, 0.418 mmol) and carbon disulphide (0.025 mL, 0.418 mmol) and allowed the reaction mixture to stir at 0 °C for 4 hours. Ethylchloroformate (0.39 mL, 0.418 mL) was then added to the reaction mixture and allowed to stir for another 1 hour at the same temperature. The reaction mixture was diluted with ethyl acetate (20 mL), washed with water followed by brine, and dried over sodium sulphate. Evaporated the organic layer under vacuum and passed the residue through a column of silicagel (50% ethyl acetate/pet.ether) and refluxed the compound attained in methanol (15 mL) for 12 hours. Methanol was removed on a rotavapor and the residue was purified by column chromatography over silica gel (40% ethyl acetate/pet.ether) to get the title compound (60 mg, 63%),.

Melting Point: 210 °C.

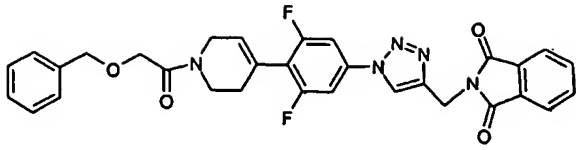
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.11 (s, 1H), 7.42-7.30 (m, 3H), 7.25 (merged with $CDCl_3$ peak, 1H), 6.90-6.82 (m, 1H), 6.02-5.90 (m, 1H), 4.91(d, J = 5.7 Hz, 2H), 4.70-4.50 (m, 1H), 4.48-4.32 (m, 1H), 4.20-4.00(m, 2H), 4.00 (s, 3H), 2.67 (m, 2H)

IR (KBr): 3408, 1628, 1029, 762 cm^{-1}

CI-MS (m/e): 505 (M+1), 473, 441

Example 73:

2-(1-{4-[1-(2-Benzyloxy-acetyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3] triazol-4-ylmethyl)-isoindole-1,3-dione



To a solution of 2-{1-[3,5-difluoro-4-(1,2,3,6-tetrahydro-pyridin-4-yl)-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl}-isoindole-1,3-dione (350 mg, 0.831 mmol), obtained in example 42, was added dry dichloromethane (10 mL), triethylamine (0.346 mL, 2.49 mmol) and reaction mixture was cooled down to 0 °C.. Benzyloxy acetylchloride (0.155 mL, 0.997 mmol) was added at this temperature and the reaction mixture was left to stir at 25-35 °C for 12 hours. It was then diluted with chloroform (25 mL), washed with water followed by brine, and dried over sodium sulphate. The chloroform layer was evaporated on rotavapor and the residue was chromatographed over silica gel (55% ethyl acetate/pet.ether) to obtain the desired product as a white solid (430 mg, 91%)

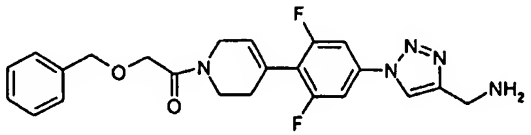
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.02 (s, 1H), 7.98-7.81 (m, 2H), 7.81-7.68 (m, 2H), 7.40-7.20 (m, 7H), 6.00-5.80 (m, 1H), 5.07 (s, 2H), 4.63 (s, 2H), 4.30-4.10(m, 1H), 4.30 (s, 3H), 3.90-3.79 (m, 1H), 3.78-3.60 (m, 1H), 2.50-2.39 (m, 2H)

IR (KBr): 1723, 1634, 1455, 1100, 719 cm^{-1}

CI-MS (m/e): 570 (M+1), 464, 174

Example 74:

1-{4-[4-(4-Aminomethyl-[1,2,3]triazol-1-yl)-2,6difluoro-phenyl]-3,6-dihydro-pyridin-1-yl]-2-benzyloxyethanone :



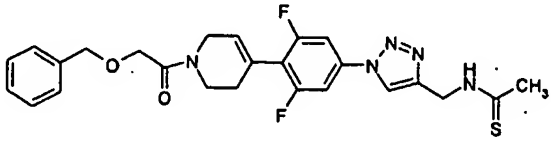
To a solution of 2-(1-{4-[1-(2-benzyloxy-acetyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-isoindole-1,3-dione (130 mg, 0.228 mmol), obtained in example 73, in methanol (5 mL) was added hydrazine hydrate (0.1 mL) and refluxed the reaction mixture for 2 hours. Allowed the reaction mixture to stir for 8 hours at 25-35 °C. Filtered the precipitate over a celite pad and concentrated the filtrates under reduced pressure. The residue was chromatographed over silica gel (5% methanol/chloroform) to obtain the required product (70 mg, 70%)

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.93 (s, 1H), 7.47-7.16 (m, 7H), 6.02-5.80 (m, 1H), 4.64 (s, 2H), 4.34-4.02 (m, 4H), 4.22 (s, 2H), 3.91-3.76 (m, 1H), 3.76-3.63 (m, 1H), 2.54-2.36 (m, 2H)

IR (KBr): 3361, 2926, 1633, 1453, 1032, 858, 752 cm^{-1}

Example 75:

***N*-(1-{4-[1-(2-Benzyloxy-acetyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thioacetamide**



To a solution of 1-{4-[4-(4-aminomethyl-[1,2,3]triazol-1-yl)-2,6-difluoro-phenyl]-3,6- dihydro-pyridin-1-yl]-2-benzyloxyethanone (125 mg, 0.285 mmol), obtained in example 74, in THF (10 mL) was added triethylamine (0.059 mL, 0.427mmol). Cooled the reaction mixture to 0 °C and added ethyl dithioacetate (0.036 mL, 0.313 mmol) and then allowed the reaction mixture to stir at 25-35 °C for 12 hours. Evaporated the solvent on rotavapor and purified the residue by column chromatography over silica gel (40% ethyl acetate/pet.ether) to get the title compound as a white solid (70 mg, 50%). Melting Point: 125 °C

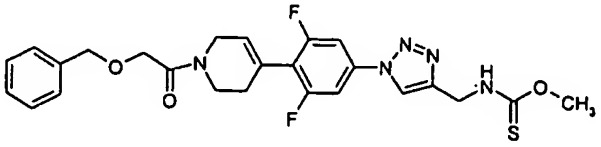
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.58-8.44 (bs, 1H), 8.16 (s, 1H), 7.40-7.20 (m, 7H), 6.00-5.82 (m, 1H), 5.01 (d, J = 5.4 Hz, 2H), 4.63 (s, 2H), 4.28-4.18 (m, 2H), 4.26 (s, 2H), 3.86-3.78 (m, 1H), 3.78-3.67 (m, 1H), 2.60 (s, 3H), 2.58 (m, 2H)

IR (KBr): 3242, 1634, 1453, 1217, 1039, 756 cm^{-1}

CI-MS (m/e): 498 (M+1)

Example 76:

(1-{4-[1-(2-Benzyloxy-acetyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester



To an ice cooled solution of 1-{4-[4-(4-aminomethyl-[1,2,3]triazol-1yl)-2,6-difluoro- phenyl]-3,6-dihydro-pyridin-1-yl]-2-benzyloxyethanone (220 mg, 0.50 mmol),

obtained in example 74, in dry THF (15 mL) was added triethylamine (0.123 mL, 0.89 mmol) and carbon disulphide (0.054 mL, 0.89 mmol) and allowed the reaction mixture to stir at 0 °C for 4 hours. Ethylchloroformate (0.085 mL, 0.89 mL) was then added to the reaction mixture and allowed to stir for further 1 hour at the same temperature. The reaction mixture was then diluted with ethyl acetate (50 mL), washed with water followed by brine and dried over sodium sulphate. Evaporated the organic layer on rotavapor and passed the residue through a column of silica gel to remove minor impurities. The resulting isothiocyanate derivative was refluxed in methanol (15 mL) for 12 hours. Methanol was removed under vacuum and the residue was purified by column chromatography over silica gel (50% ethyl acetate/pet.ether) to afford the title compound as a pale yellow semisolid (70 mg, 65%).

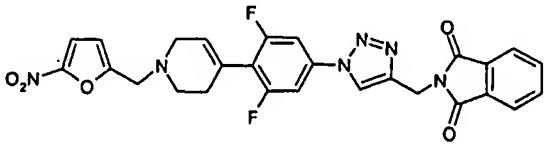
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.12 (s, 1H), 7.44-7.18 (m, 7H), 7.00-6.85 (m, 1H), 6.08-5.82 (m, 1H), 4.93 (d, J = 6.1 Hz, 2H), 4.64 (m, 2H), 4.26 and 4.12 (two s, 3H, rotamers in 4:1 raio), 4.23-4.18 (m, 1H), 4.00 (s, 2H), 3.92-3.82 (m, 1H), 3.80-3.62 (m, 1H), 3.58-3.40 (m, 1H), 2.58-2.40 (m, 2H).

IR (KBr): 3393, 2927, 1632, 1511, 1453, 1364, 1201, 1041, 858, 751 cm^{-1}

CI-MS (m/e): 514 (M+1), 482.

Example 77:

2-(1-[3,5-Difluoro-4-[1-(5-nitro-furan-2-ylmethyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-isoindole-1, 3-dione



To a suspension of 2-{1-[3,5-difluoro-4-(1,2,3,6-tetrahydro-pyridin-4-yl)-phenyl]-1*H*-[1,2,3]triazol-4-yl methyl}-isoindole-1,3-dione (0.2 grams, 0.425 mmol) in dry THF (15 mL) was added molecular sieves (4 A^0) followed by 5-nitro-2-furfural (87 mg, 0.618 mmol), obtained in example 42. The reactiom mixture was stirred at 25-35 °C for 1.5 hours. Sodium triacetoxy borohydride (0.402 gram, 1.900 mmol) was added to the reaction mixture and then allowed to stir 9 to 13 hours at ambient temperature. The reaction mixture was filtered and the residue was washed with dichloromethane. The organic layer was then washed with water and dried over sodium sulphate. The solvent

was evaporated and the residue was purified by column chromatography over silica gel (40% ethyl acetate/pet.ether) to give the desired product as a white solid (95 mg, 37%).

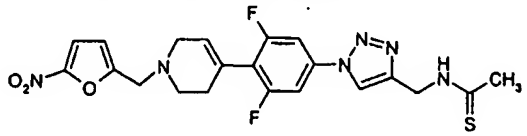
^{1}H NMR (CDCl3, 200 MHz): δ 8.01(s, 1H), 7.94-7.82 (m, 2H), 7.82-7.68 (m, 2H), 7.40-7.28 (m, 3H), 6.55 (d, J = 3.4 Hz, 1H), 5.92-5.84 (m, 1H), 5.08 (s, 2H), 3.81 (s, 2H), 3.36-3.24 (m, 2H), 2.83(t, J = 5.6Hz, 2H), 2.58-2.44 (m, 2H)

IR (KBr): 3431, 3132, 2925, 2854, 1717, 1493, 1395, 1244 cm^{-1}

CI-MS (m/e): 547 (M+1), 422, 295, 222

Example 78

***N*-(1-{3,5-Difluoro-4-[1-(5-nitro-furan-2-ylmethyl)-1,2,3,6-tetrahydro-pyridin-4-yl] phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thioacetamide**



2-(1-[3,5-Difluoro-4-[1-(5-nitro-furan-2-ylmethyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-isoindole-1,3-dione (95 mg, 0.174 mmol), obtained in example 77, was suspended in methanol and hydrazine hydrate (0.07 mL) was added to the reaction mixture. It was refluxed for 2 hours and brought to 25-35 °C and stirred for 4 hours. The reaction mixture was filtered and the residue washed with 5% methanol/chloroform (30 mL). The filtrate was then concentrated and the residue purified by column chromatography over silica gel (10% methanol/chloroform) to yield (1-{3,5-difluoro-4-[1-(5-nitro-furan-2-ylmethyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-phenyl}-1*H*-[1,2,3]triazol-4-yl)methylamine as a cream colour sticky solid (40 mg). The amine prepared by following afore mentioned method (225 mg, 0.54 mmol) was taken in THF (10 mL) and cooled to 0 °C. To the reaction mixture added triethylamine (0.15 mL, 1.08 mmol) followed by ethyl dithioacetate (0.07 mL, 0.649 mmol) and stirred for 10 hours at 25-35 °C. The reaction mixture was concentrated under vacuum and purified by column chromatography over silica gel (2 % methanol/chloroform) to afford the title compound as a white solid (110 mg, 43%)

Melting Point: 120-122 °C

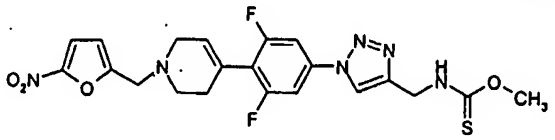
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.12 (s, 1H), 7.99-7.90 (m, 1H), 7.40-7.28 (m, 3H), 6.56 (d, J = 3.5 Hz, 1H), 5.96-5.84 (m, 1H), 5.02 (d, J = 6.0 Hz, 2H), 3.83 (s, 2H), 3.36-3.28 (m, 2H), 2.85 (t, J = 5.5 Hz, 2H), 2.60 (s, 3H), 2.60-2.46 (m, 2H)

IR (KBr): 3431, 2925, 2855, 1626, 1502 cm^{-1}

CI-MS (m/e): 475 (M+1), 444, 350, 346

Example 79:

(1-{3,5-Difluoro-4-[1-(5-nitro-furan-2-ylmethyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester



(1-{3,5-difluoro-4-[1-(5-nitro-furan-2-ylmethyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-phenyl}-1*H*-[1,2,3]triazol-4-yl)methylamine (225 mg, 0.910 mmol), was taken in THF (15 mL) and cooled to 0 °C. To the reaction mixture was added triethylamine (0.14 mL, 1 mmol) followed by carbon disulphide (0.11 mL, 1.82 mmol) and allowed to stir for 4 hours at 0 °C. Ethyl chloroformate (0.09 mL, 0.190 mmol) was then added to the reaction mixture and stirred for another 1 hour. The reaction mixture was then warmed to 25-35 °C and concentrated under vacuum. The residue was chromatographed over silica gel (2% methanol/chloroform) and resulting isothiocyanate derivative was refluxed in methanol for 16 hours. Reaction mixture was concentrated and the residue was purified by column chromatography over silica gel (1% methanol/chloroform) to yield the desired compound as a white solid (65 mg, 26%)

Melting Point: 156-158 °C.

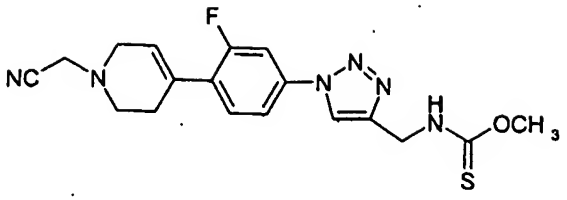
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.01 (s, 1H), 7.40-7.26 (m, 3H), 6.94-6.80 (m, 1H), 6.55 (d, J = 3.5 Hz, 1H), 5.96-5.84 (m, 1H), 4.92 (d, J = 5.9 Hz, 2H), 4.00 (s, 3H), 3.82 (m, 2H), 3.38-3.24 (m, 2H), 2.84 (t, J = 5.5 Hz, 2H), 2.58-2.42 (m, 2H)

IR (KBr): 3426, 2925, 1502, 1456, 1351 cm^{-1}

CI-MS (m/e): 491 (M+1), 459, 366

Example 80:

{1-[4-(1-cyanomethyl-1, 2, 3, 6-tetrahydro-pyridinyl)-3-fluoro-phenyl]-1H-[1, 2, 3] triazol-4-ylmethyl}-thiocarbamic acid O-methyl ester



To a solution of [4-{4-azido-phenyl}-3, 6-dihydro-2H-pyridin-1-yl]-acetonitrile (0.04 grams, 0.16 mmol), obtained in preparation 26, in dry DMF (2 mL) was added N-Ethyldiisopropylamine (0.02 grams, 0.16 mmol), prop-2-ynyl-thiocarbamic acid-O-methyl ester (0.02 grams, 0.18 mmol) and copper iodide (0.015 grams, 0.08 mmol) were added. The reaction mixture was allowed to stir for 20 minutes at 25-35 °C. It was then diluted with ethyl acetate (4 mL) and washed with an aqueous solution of ammonium chloride and ammonium hydroxide (1:1). The organic solvent was removed under vacuum and the residue was purified using column chromatography (0.2:1 ethyl acetate/pet. Ether) to give the title compound as a white crystalline solid (0.04 grams, 65%)

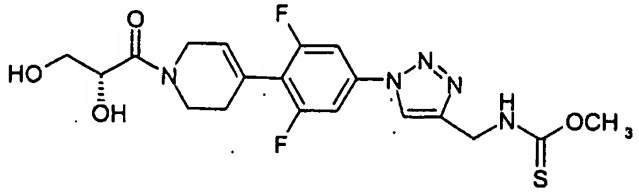
^{1}H NMR ($CDCl_3$, 200MHz): δ 8.19 & 7.90(two s, 1H , rotamers in the ratio 4:1,), 7.60-7.36(m, 3H), 7.00-6.82(m, 1H), 6.17-6.00 (m, 1H), 4.92 and 4.66 (2d, J=6.4 Hz, 2H, rotamers in 4:1 ratio), 4.12 & 4.00 (two s, 3H, rotamers in the ratio 1:3), 3.69 (s, 2H), 3.42-3.35 (m, 2H), 2.90 (t, J=5.4 Hz, 2H), 2.75-2.60 (m, 2H).

IR (Neat): 2924, 1515, 1459, 123e0, 1146, 1045, 978, 875, 757 cm^{-1}

CI-MS (m/e): 387(M+1)

Example 81:

(1-{4-[1-(2(R), 3-Dihydroxy-propionyl)-1, 2, 3, 6-tetrahydro-pyridin-4-yl]-3,5-difluoro-phenyl}-1H-[1, 2, 3] triazol-4-ylmethyl)-thiocarbamic acid 0-methyl ester



(1-{4-[1-((4R)-2-2-Dimethyl-[1, 3] dioxolane-4-carbonyl)-1, 2, 3, 6-tetrahydro-pyridin-4-yl)-3, 5-diflouro-phenyl}-1H-[1, 2, 3] triazol-4-yl-methyl)-thiocarbamic acid O-methyl ester (300 mg, 0.61 mmol), obtained in example 59, was reacted using the same procedure as for (1-{4-[1-(2(S), 3-Dihydroxy-propionyl)-1, 2, 3, 6-tetrahydro-pyridin-4-

yl]-3-fluoro-phenyl}-1H-[1, 2, 3] triazol-4-ylmethyl)-thiocarbamic acid-O-methyl ester (Example 61) to yield the desired product (130 mg, 47%).

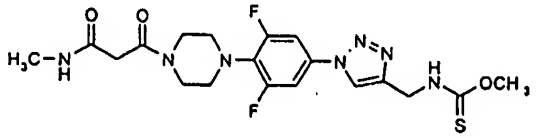
^{1}H NMR ($CDCl_3$, 200MHz): δ 9.63-9.52(m, 1H), 8.78 and 8.70 (two s, rotamers in the ratio 3:1, 1H), 7.77 (d, J=7.8Hz, 2H), 6.02-5.85 (m, 1H), 4.99-4.88(m, 1H), 4.80-4.58 (m, 3H), 4.50-4.23(m, 3H), 4.23-4.10 (m, 1H), 3.96 and 3.89 (two s, rotamers is the ratio 1:3, 3H), 3.96-3.65 (m, 1H), 3.65-3.40 (m, 2H), 2.58-2.30 (m, 2H)

IR (Neat): 3345, 2943, 1630, 1512, 1453, 1201, 1048, 756, 619 cm^{-1}

CI-MS (m/e): 454 (M+1), 422 $(M-31)^+$

Example 82:

(1-{3,5-Difluoro-4-[4-(2-methylcarbamoyl-acetyl)-piperazin-1-yl]-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



The title compound was prepared in 72% yield from 3-[4-(4-azido-2,6-difluoro-phenyl)- piperazin-1-yl]-N-methyl-3-oxo-propionamide (80 mg, 0.24 mmol), obtained in preparation 36, and prop-2-ynyl-thiocarbamic acid-O-methyl ester (37 mg, 0.29 mmol) by following the same procedure as described in example 1.

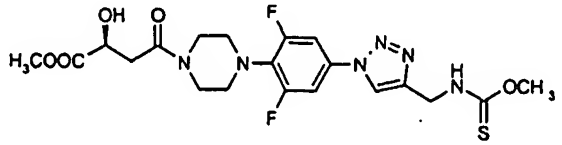
^{1}H NMR ($CDCl_3$ + CD_3OD, 400 MHz): δ 8.91 and 8.82 (2t, J = 5.5 Hz, 1H, rotamers in the ratio 1:3), 8.25 and 8.13 (2s, 1H, rotamers in the ratio 4:1), 7.65 (bs, 1H), 7.40 (d, J = 9.4 Hz, 2H, rotamers in the ratio 3:1), 4.85 and 4.58 (2s, 3H, rotamers in the ratio 1:3), 3.76(t, J = 4.8 Hz, 2H), 3.71 (t, J = 4.6 Hz, 2H), 3.39 (s, 2H), 3.37-3.19 (m, 4H), 2.79 (d, J = 4.8 Hz, 3H).

IR (KBr): 3354, 2924, 1648, 1629, 1516, 1466, 1201, 1036, 858 cm^{-1}.

ES-MS (m/e): 490 (M^++ 23), 468 (M^++1)

Example 83:

4-(4-{2,6-Difluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazin-1-yl)-2(S)- hydroxy-4-oxo-butyric acid methyl ester



The title compound was prepared from 2-hydroxy-succinic acid 1-methyl ester (483 mg, 3.26 mmol) and [1-(3,5-Difluoro-4-piperazin-1-yl-phenyl)-1H-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid O-methyl ester (1 gram, 2.72 mmol), obtained in example 6, by following the same procedure as described in example 27.

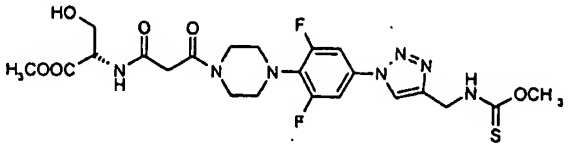
^{1}H NMR (DMSO, 400 MHz): δ 9.67 – 9.62 (m, 1H), 8.72 and 8.67 (2s, 1H, rotamers in the ratio 3:1), 7.75 (d, J = 10.1 Hz, 2H), 5.54 (d, J = 6.3 Hz, 1H), 4.72 and 4.36 (2d, J = 5.5 Hz, 2H, rotamers in the ratio 2:1), 4.50 – 4.39 (m, 1H), 3.94 and 3.89 (2s, 3H, rotamers in the ratio 1:3), 3.64 (s, 3H), 3.59 – 3.56 (m, 4H), 3.20 – 3.18 (m, 2H), 3.18 - 3.10 (m, 2H), 2.75 (d, 6.0 Hz, 2H).

IR (KBr): 3271, 2923, 1737, 1638, 1518, 1444, 1267, 1207, 856 cm^{-1}.

CI-MS (m/e): 499 (M^++1), 467

Example 84:

2(S)-[3-(4-{2,6-Difluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazin-1-yl)-3-oxo-propionylamino]-3-hydroxy-propionic acid methyl ester



The title compound was obtained from 2(S)-{3-[4-(4-azido-2,6-difluoro-phenyl)-piperazin-1-yl]-3-oxo-propionylmino}-3-hydroxy-propionic acid methyl ester (200 mg, 0.47 mmol), obtained in preparation 37, by following the procedure as described in example 1.

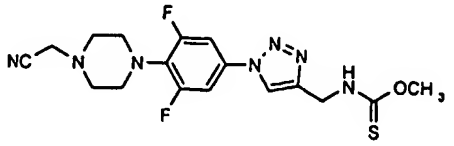
^{1}H NMR (DMSO, 400 MHz): δ 9.99 – 9.61 (m, 1H), 8.72 and 8.67 (2s, 1H, rotamers in the ratio 3:1), 8.44 (d, J = 7.8 Hz, 1H), 7.74 (d, J = 9.9 Hz, 2H), 5.06 (t, J = 5.6Hz, 1H), 4.72, 4.43 (d, J = 5.6 Hz, 2H, rotamers in the ratio 3:1), 4.40 – 4.36(m, 1H), 3.95 and 3.89 (2s, 3H, rotamers in the ratio 1:3), 3.75 – 3.98 (m, 2H), 3.64 (s, 3H), 3.62 – 3.51 (m, 4H), 3.46 (d, J = 6.9 Hz, 2H), 3.19 – 3.17 (m, 2H), 3.16 – 3.10 (m, 2H).

IR (KBr): 3285, 1739, 1654, 1521, 1447.2, 1228, 1035, 859 cm^{-1}.

CI-MS (m/e): 556 (M^++1), 538, 524, 506

Example 85:

{1-[4-(4-Cyanomethyl-piperazin-1-yl)-3,5-difluoro-phenyl]-1H-[1,2,3]triazol-4-ylmethyl}-thiocarbamic acid O-methyl ester



The title compound (400 mg, 27%) was synthesized from 4-(4-azido-2,6-difluoro-phenyl)-piperazine-1-carbonitrile (1 gram, 3.6 mmol), obtained in preparation 38, by following the procedure as described in example 1.

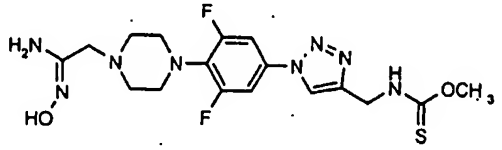
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04 and 7.80 (2s, 1H, rotamers in the ratio 4:1), 7.28 (d, J = 9.8 Hz, 2H), 6.92 (bs, 1H), 4.90 and 4.65 (2d, J = 5.8 Hz, 2H, rotamers in the ratio 4:1), 4.12, 3.99 (2s, 3H, rotamers in the ratio 1:4), 3.59 (s, 2H), 3.35 – 3.21 (m, 4H), 2.74 (t, J = 4.7 Hz, 4H).

IR (KBr): 3432, 2923, 1630, 1517, 1454, 1353, 1288, 1212, 1131, 1027, 856, 617, 527 cm^{-1}.

CI-MS (m/e): 376 (M^+-31), 349

Example 86:

(1-{3,5-Difluoro-4-[4-(N-hydroxycarbamimidoylmethyl)-piperazin-1-yl]-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



To a stirred solution of {1-[4-(4-cyanomethyl-piperazin-1-yl)-3,5-difluoro-phenyl]-1H-[1,2,3]triazol-4-ylmethyl}-thiocarbamic acid O-methyl ester (350 mg, 0.86 mmol), obtained in example 85, in ethanol (20 mL) was added hydroxylamine hydrochloride (239 mg, 3.44 mmol) and sodium carbonate (274 mg, 2.58 mmol) in minimum amount of water and refluxed for 9 to 13 hours at 60–70 °C. Ethanol was removed under vacuum and the residue was diluted with ethylacetate (20 mL) and washed with water, brine and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by column chromatography (7:3 ethyl acetate/pet ether) to give the title compound (80 mg, 21%).

^{1}H NMR (DMSO, 400 MHz): δ 9.65 – 9.61 (m, 1H), 8.98 (s, 1H), 8.70 and 8.66 (2s, 1H,rotamers in the ratio 4:1), 7.71 (d, J = 9.9 Hz, 2H), 5.25 (s, 2H), 4.72 and 4.43 (2d, J =

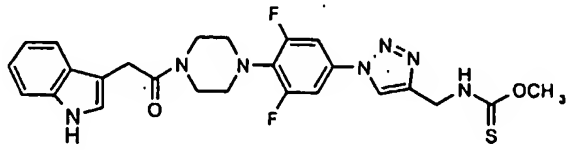
5.6 Hz, 2H, rotamers in the ratio 4:1), 3.94 and 3.88 (2s, 3H, rotamers in the ratio 1:4), 3.29 – 3.16 (m, 4H), 2.91 (s, 2H), 2.52 – 2.49 (m, 4H).

CI-MS (m/e): 441 (M^++1), 425, 393, 369, 337

IR (KBr): 3394, 2924, 1672, 1517, 1458, 1228, 1144, 1036, 860 cm^{-1}.

Example 87:

(1-{3,5-Difluoro-4-[4-(2-1H-indol-3-yl-acetyl)-piperazin-1-yl]-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



The title compound (130 mg, 54 %) was synthesized from (1H-indol-3-yl)-acetic acid (81 mg, 0.46 mmol) and [1-(3,5-difluoro-4-piperazin-1-yl-phenyl)-1H-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid O-methyl ester, obtained in example 6, by following the procedure as described in example 27.

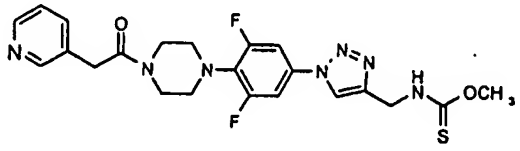
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.09 (s, 1H), 8.01 and 7.76 (2s, 1H, rotamers in the ratio 4:1), 7.64 (d, J = 8.1 Hz, 1H), 7.38 (d, J = 8.1 Hz, 1H), 7.29 – 7.13 (m, 5H), 6.84 (bs, 1H), 4.90 and 4.64 (d, J = 5.9 Hz, 2H, rotamers in the ratio 4:1), 4.11 and 3.99 (2s, 3H, rotamers in the ratio 1:6), 3.90 (s, 2H), 3.82 – 3.78 (m, 2H), 3.63 – 3.58 (m, 2H), 3.23 – 3.18 (m, 2H), 3.10 – 3.01 (m, 2H).

IR (KBr): 3409, 2929, 1629, 1518, 1450, 1218, 1148, 1034, 856, 745 cm^{-1}.

ES-MS (m/e): 548 (M^++ 23), 526 (M^++1)

Example 88:

(1-{3,5-Difluoro-4-[4-(2-pyridin-3-yl-acetyl)-piperazin-1-yl]-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



The title compound (150 mg, 58%) was synthesized from 1-[4-(4-azido-2,6-difluoro-phenyl)- piperazin-1-yl]-2-pyridin-3-yl-ethanone (190 mg, 0.53 mmol), obtained in preparation 39, by following the procedure as described in example 1.

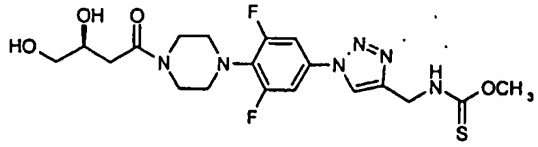
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.56 – 8.51 (m, 2H), 8.04 and 7.79 (2s, 1H, rotamers in the ratio 3:1) 7.66 (dd, J_1 = 1.9 Hz, J_2 = 6.0 Hz, 1H), 7.33 – 7.26 (m, 3H), 6.94 (bs, 1H), 4.90 and 4.65 (2d, J = 5.9 Hz, 2H, rotamers in the ratio 4:1), 4.11 and 3.99 (2s, 3H, rotamers in the ratio 1:5), 3.81 – 3.79 (m, 2H), 3.77 (s, 2H), 3.63 (t, J = 4.8 Hz, 2H), 3.22 – 3.20 (m, 2H), 3.19 – 3.14 (m, 2H).

IR (KBr): 3135, 2857, 1646, 1582, 1521, 1438, 1205, 1147, 1032, 850 cm^{-1}.

ES-MS (m/e): 510 (M^++ 23), 489 (M^++2)

Example 89:

(1-{4-[4-(3(S),4-Dihydroxy-butyryl)-piperazin-1-yl]-3,5-difluoro-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



To a stirred solution of 4-(4-{2,6-difluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazin-1-yl)-2(S)-hydroxy-4-oxo-butyric acid methyl ester (100 mg, 0.2 mmol), obtained in example 83, in methanol was added sodium borohydride (16 mg, 63.6 %) portion wise at 0 °C. The reaction mixture was stirred for 6 hours at same temperature. Methanol was removed under vacuum and the residue was purified by column chromatography (2% methanol/chloroform) to yield the title compound (60 mg, 64%).

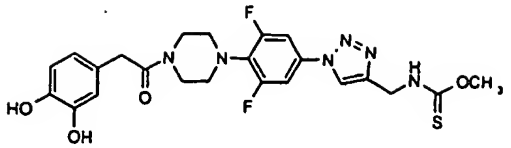
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 and 7.80 (2s, 1H, rotamers in the ratio 5:1), 7.31 (d, J = 9.1 Hz, 2H), 6.96 – 6.82 (m, 1H), 4.90 and 4.65 (2d, J = 6.2 Hz, 2H, rotamers in the ratio 4:1), 4.22 – 4.16 (m, 1H), 4.11 and 4.00 (2s, 3H, rotamers in the ratio 1:6), 3.78 – 3.73 (m, 3H), 3.62 – 3.56 (m, 3H), 3.25 – 3.19 (m, 4H), 2.64 – 2.52 (m, 2H).

IR (KBr): 3358, 2924, 1624, 1500, 1445, 1229, 1033, 857, 754 cm^{-1}.

CI-MS (m/e): 471 (M^++1), 453, 439, 421

Example 90:

[1-(4-{4-[2-(3,4-Dihydroxy-phenyl)-acetyl]-piperazin-1-yl}-3,5-difluoro-phenyl)-1H-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid O-methyl ester



The title compound (200 mg, 57%) was synthesized from (3,4-dihydroxy-phenyl)-acetic acid (114 mg, 0.68 mmol) and [1-(3,5-difluoro-4-piperazin-1-yl-phenyl)-1H-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid O-methyl ester, obtained in example 6, by following the procedure as described in example 27.

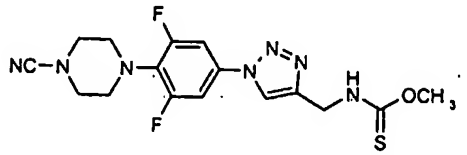
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03 and 7.83 (2s, 1H, rotamers in the ratio 4:1), 7.25 (d, J = 8.9 Hz, 2H), 7.05 (t, J = 5.9 Hz, 1H), 6.88 (d, J = 1.9 Hz, 1H), 6.80 (d, 8.1Hz, 1H), 6.60 (dd, J_1 = 1.9 Hz, J_2 = 8.1 Hz, 1H), 4.89 and 4.66 (2d, J = 6.2 Hz, 2H, rotamers in the ratio 5:1), 4.11 and 3.99 (2s, 3H, rotamers in the ratio 1:4), 3.78 (t, J = 4.6 Hz, 2H), 3.69 (s, 2H), 3.61 (t, J = 4.6 Hz, 2H), 3.22 – 3.18 (m, 2H), 3.12 – 3.06 (m, 2H).

IR (KBr): 3255, 1624, 1519, 1445, 1282, 1231, 1035, 858 cm^{-1}.

ES-MS (m/e): 519 (M^++1), 541 (M^++ 23).

Example 91:

{1-[4-(4-Cyano-piperazin-1-yl)-3, 5- difluoro-phenyl]-1H-[1,2,3]triazol- 4-ylmethyl}-thiocarbamic acid O-methyl ester



To a solution of [1-(3,5-difluoro-4-piperazin-1-yl-phenyl)-1H-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid O-methyl ester (500 mg, 1.36 mmol), obtained in example 6, and sodium acetate (602 mg, 7.34 mmol) in methanol (40 mL) was treated during 5 minutes, with a methanol (10 mL) solution of cyanogen bromide (173 mg, 1.63 mmol) at 0 °C and stirred at same temperature for 2 hours. The methanol was removed under vacuum and the residue was washed with sodium bicarbonate and extracted with dichloromethane (DCM) and washed with water, dried over Na_2SO_4 and concentrated and purified by column chromatography (3:7 ethyl acetate/petroleum ether) to give the title compound (120 mg, 23%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 and 7.80 (2s, 1H, rotamers in the ratio 4:1), 7.31 (d, J = 9.1 Hz, 2H), 6.95 – 6.85 (m, 1H), 4.90 and 4.65 (2d, J = 5.9 Hz, 2H, rotamers in the

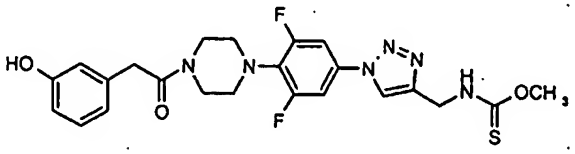
ratio 4:1), 4.11 and 3.99 (2s, 3H, rotamers in the ratio 1:5), 3.40 – 3.37 (m, 4H), 3.36 – 3.30 (m, 4H).

IR (KBr): 3283, 2215, 1518, 1451, 1384, 1331, 1204, 1139, 1040, 857, 756 cm^{-1}.

CI-MS (m/e): 394 (M^++1), 362, 275

Example 92:

[1-(3,5-Difluoro-4-{4-[2-(3-hydroxyphenyl)-acetyl]-piperazin-1-yl}-phenyl)-1H-[1,2,3]triazol-4-ylmethyl] -thiocarbamic acid O-methyl ester



The title compound (220 mg, 68%) was synthesized from 1-[4-(4-azido-2,6-difluoro-phenyl)-piperazin-1-yl]-2-(3-hydroxy-phenyl)-ethanone (240 mg, 0.64 mmol), obtained in preparation 40, by following the procedure as described in example 1.

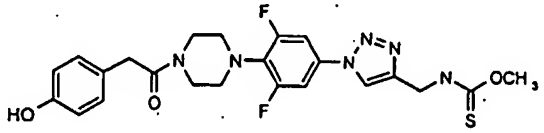
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03 and 7.81 (2s, 1H, rotamers in the ratio 4:1), 7.27 – 7.17 (m, 3H), 7.00 – 6.89 (m, 1H), 6.84 (s, 1H), 6.79 – 6.74 (m, 2H), 4.90, 4.65 (2d, J = 6.2 Hz, 2H, rotamers in the ratio 4:1), 4.11, 3.99 (2s, 3H, rotamers in the ratio 1:4), 3.81 – 3.76 (m, 2H), 3.75 (s, 2H), 3.61 – 3.58 (m, 2H), 3.20 – 3.17 (m, 2H), 3.10 – 3.00 (m, 2H).

IR (KBr): 3284, 1627, 1518, 1456, 1230, 1151, 1036, 857, 774 cm^{-1}.

ES-MS (m/e): 503 (M^++1)

Example 93:

[1-(3,5-Difluoro-4-{4-[2-(4-hydroxyphenyl)-acetyl]-piperazin-1-yl}-phenyl)-1H-[1,2,3]triazol-4-ylmethyl] -thiocarbamic acid O-methyl ester



The title compound (79 mg, 40%) was synthesized from 1-[4-(4-azido-2,6-difluoro-phenyl)-piperazin-1-yl]-2-(4-hydroxy-phenyl)-ethanone (150 mg, 0.40 mmol), obtained in preparation 41, by following the procedure as described in example 1.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03 and 7.78 (2s, 1H, rotamers in the ratio 5:1), 7.28 (d, J = 9.5 Hz, 2H), 7.13 (d, J = 8.6 Hz, 2H), 6.88 – 6.83 (m, 1H), 6.80 (d, J = 8.6 Hz, 2H), 5.02 (s, 1H), 4.90 and 4.65 (2d, J = 5.9 Hz, 2H, rotamers in the ratio 4:1), 4.11 and 3.99

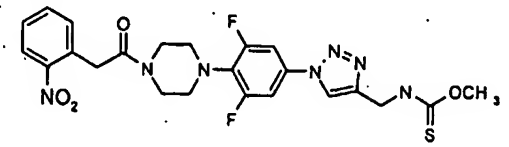
(2s, 3H, rotamers in the ratio 1:4), 3.77 (t, J = 4.8 Hz, 2H), 3.70 (s, 2H), 3.61 – 3.56 (m, 2H), 3.22 – 3.18 (m, 2H), 3.10 – 3.02 (m, 2H).

IR (KBr): 3380, 2923, 1624, 1516, 1444, 1231, 1149, 1035, 857 cm^{-1}.

CI-MS (m/e): 471 (M^+-31), 384, 107

Example 94:

[1-(3,5-Difluoro-4-{4-[2-(2-nitro-phenyl)-acetyl]-piperazin-1-yl}-phenyl)-1H-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid O-methyl ester



The title compound (450 mg, 79%) was synthesized from 1-[4-(4-azido-2,6-difluoro-phenyl)-piperazin-1-yl]-2-(2-nitro-phenyl)-ethanone (430 mg, 1.07 mmol) obtained in preparation 42, by following the same procedure as described in example 1.

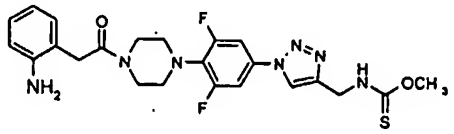
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.13 and 8.11 (dd, J_1=1.1 Hz, J_2 = 8.3 Hz, 1H), 8.04 and 7.80 (2s, 1H, rotamers in the ratio 3:1), 7.62-7.58(m, 1H), 7.47(t, J = 7.0 Hz, 1H), 7.37(d, J = 7.5 Hz, 1H), 7.31 (d, J = 9.4 Hz, 2H), 6.92-6.88 (m, 1H), 4.91 and 4.65(2d, J=5.9Hz, 2H, rotamers in the ratio 4:1), 4.12 (s, 2H), 4.00 (s,3H), 3.82-3.76 (m, 2H), 3.75-3.69(m, 2H), 3.39-3.30(m, 2H), 3.30-3.21(m, 2H).

IR (KBr): 3267, 1640, 1522, 1444, 1340, 1206, 1141, 1031, 859, 730 cm^{-1}.

CI-MS (m/e): 500 (M^+-31), 383, 337

Example 95:

[1-(4-{4-[2-(2-Amino-phenyl)-acetyl]-piperazin-1-yl}-3, 5-difluoro-phenyl)-1H-[1, 2,3] triazol-4-ylmethyl]-thiocarbamic acid O-methyl ester



To a stirred solution of [1-(3,5-difluoro-4-{4-[2-(2-nitro-phenyl)-acetyl]-piperazin-1-yl}-phenyl)-1H-[1,2,3] triazol-4-ylmethyl]-thiocarbamic acid O-methyl ester (200 mg, 0.38 mmol), obtained in example 94, and ammonium chloride (202 mg, 3.8 mmol) in ethanol: water (2:1) solution was heated to 80–90 °C and then added iron (63 mg, 1.13 mmol) portion wise and heated at same temperature for 3 hours. Ethanol was removed

under vacuum and the reaction mixture was extracted with ethylacetate. The organic layer was washed with water (2 x 20 mL), brine and dried over Na_2SO_4. The organic layer was concentrated under vacuum and the residue was purified by column chromatography (1% $CH_3OH/CHCl_3$) to give the title product (135 mg, 72 %).

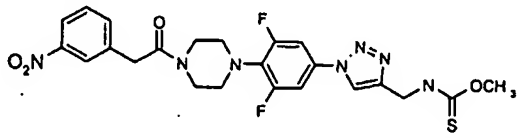
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03 and 7.78 (2s, 1H, rotamers in the ratio 5:1), 7.32 – 7.26 (m, 2H), 7.11 – 7.06(m, 1H), 7.03 (d, J = 7.2 Hz, 1H), 6.99 - 6.86 (m, 1H), 6.73 (d, J = 7.5 Hz, 2H), 4.90 and 4.64 (2d, J = 5.9 Hz, 2H, rotamers in the ratio 5:1), 4.11 and 3.99 (2s, 3H, rotamers in the ratio 1:5), 3.78 – 3.73 (m, 2H), 3.71 (s, 2H), 3.21 – 3.18 (m, 2H), 3.18 – 3.12 (m, 2H).

IR (KBr): 3355, 1525, 1517, 1457, 1205, 1147, 1035, 855, 753 cm^{-1}.

CI-MS (m/e): 502 (M^++1), 470, 452, 369

Example 96:

[1-(3,5-Difluoro-4-{4-[2-(3-nitro-phenyl)-acetyl]-piperazin-1-yl}-phenyl)-1H-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid O-methyl ester



The title compound (320 mg, 74 %) was synthesized from (3-nitro-phenyl)-acetic acid (148 mg, 0.82 mmol) and [1-(3,5-difluoro-4-piperazin-1-yl-phenyl)-1H-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid O-methyl ester (300 mg, 0.82 mmol), obtained in example 6, by following the procedure as described in example 27.

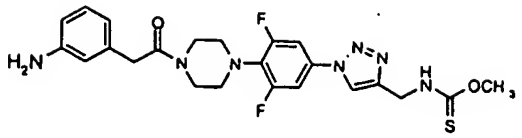
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.15 (dd, J_1 = 1.1 Hz, J_2=6.9 Hz, 2H), 8.05 and 7.81(2s, 1H, rotamers in the ratio 5:1), 7.63 (d, J=7.8 Hz, 1H), 7.55-7.51 (m, 1H), 7.31(d, J=9.1 Hz, 2H), 6.96 (t, J=5.4 Hz, 1H), 4.90 and 4.65 (2d, J=6.1Hz, 2H, rotamers in the ratio 4:1),4.11 and 3.99(2s, 3H, rotamers in the ratio 1:5), 3.87(s, 2H), 3.80 (t, J= 4.8 Hz, 2H), 3.65(t, J = 4.6 Hz, 2H), 3.25-3.18 (m, 4H).

IR (KBr): 3250, 1638, 1527, 1455, 1349, 1229, 1033, 856, 730 cm^{-1}.

CI-MS (m/e): 500 (M^+-31), 470, 443, 413

Example 97:

[1-(4-{4-[2-(3-Amino-phenyl)-acetyl]-piperazin-1-yl}-3,5-difluoro-phenyl)-1H-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid O-methyl ester



The title compound (200 mg, 71 %) was synthesized from [1-(3,5-difluoro-4-{4-[2-(3-nitro-phenyl)-acetyl]-piperazin-1-yl}-phenyl)-1H-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid O-methyl ester (300 mg, 0.56 mmol), obtained in example 96, by following the procedure as described in example 95.

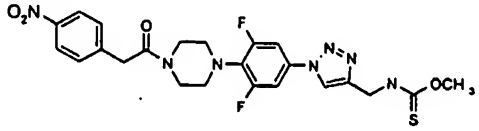
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 and 7.78(2s, 1H, rotamers in the ratio 5:1), 7.27(d, J=9.7 Hz, 2H), 7.11(t, J=8.1Hz, 1H), 6.87-6.83(m, 1H), 6.65-6.62(m, 2H), 6.58(dd, J_1 = 2.1 Hz, J_2=7.8Hz, 1H), 4.90 and 4.64(2d, J=5.9Hz, 2H, rotamers in the ratio 5:1), 4.11 and 3.99(2s, 3H, rotamers in the ratio 1:5), 3.77 (t, J=4.8 Hz, 2H), 3.69 (s, 2H), 3.56 (t, J=4.6 Hz, 2H), 3.22-3.18 (m, 2H), 3.08-3.01 (m, 2H).

IR (KBr): 3358, 2924, 1629, 1518, 1461, 1230, 1151, 1038, 858 cm^{-1}

ES-MS (m/e): 524 (M^++ 23), 502 (M^++1)

Example 98:

[1-(3,5-Difluoro-4-{4-[2-(4-nitro-phenyl)-acetyl]-piperazin-1-yl}-phenyl)-1H-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid O-methyl ester



The title compound (460 mg, 71%) was synthesized from 1-[4-(4-azido-2,6-difluoro-phenyl)-piperazin-1-yl]-2-(4-nitro-phenyl)-ethanone (490 mg, 1.22 mmol), obtained in preparation 43, by following the procedure as described in example 1.

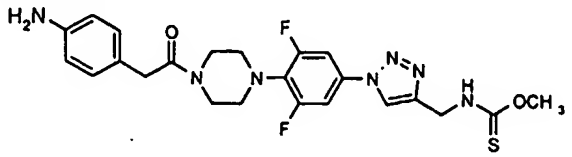
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.21 (d, J=8.6 Hz, 2H), 8.04 and 7.90 (2s, 1H, rotamers in the ratio 5:1), 7.45 (d, J = 8.6 Hz, 2H), 7.30 (d, J = 9.1 Hz, 2H), 6.92 (bs, 1H), 4.90 and 4.65(2d, , J=5.9 Hz, 2H, rotamers in the ratio 3:1), 4.11 and 3.99(2s, 3H, rotamers in the ratio 1:5), 3.87 (s, 2H), 3.79 (t, J = 4.8 Hz, 2H), 3.61(t, J = 4.6 Hz, 2H), 3.23-3.20(m, 2H), 3.18-3.15(m, 2H).

IR (KBr): 3279, 1643, 1515, 1451, 1343, 1280, 1226, 1207, 1149, 1032, 857 cm^{-1}.

CI-MS (m/e): 500 (M^+-31), 470

Example 99:

[1-(4-{4-[2-(4-Amino-phenyl)-acetyl]-piperazin-1-yl}-3,5-difluoro-phenyl]-piperazin-1-yl}-phenyl)-1H-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid O-methyl ester



The title compound (65 mg, 69 %) was synthesized from [1-(3,5-difluoro-4-{4-[2-(4-nitro-phenyl)-acetyl]-piperazin-1-yl}-phenyl)-1H-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid O-methyl ester (100 mg, 0.19 mmol), obtained in example 98, by employing the same procedure as described in example 95.

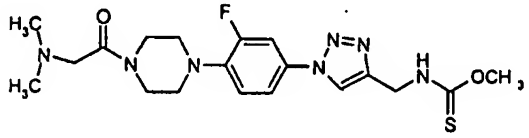
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 and 7.77(2s, 1H, rotamers in the ratio 3:1), 7.30-7.24(m, 2H), 7.04 (d, J= 8.6 Hz, 2H), 6.87(bs,1H), 6.66(d, J = 8.6 Hz, 2H), 4.90 and 4.65(2d, J= 5.9 Hz, 2H, rotamers in the ratio 4: 1), 4.11 and 3.99 (2s, 3H, rotamers in the ratio 1:5), 3.76(t, J = 4.8 Hz, 2H), 3.66(s, 2H), 3.56 (t, J=4.6 Hz, 2H), 3.20-3.18 (m, 2H), 1.70(bs,2H).

IR (KBr): 3351, 2921, 1630, 1517, 1448, 1217, 1149, 1033, 852, 688 cm^{-1}.

ES-MS (m/e): 524 (M^++ 23), 502 (M^++1)

Example 100:

(1-{4-[4-(2-Dimethylamino-acetyl)-piperazin-1-yl]-3-fluoro-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



The title compound (42 mg, 30 %) was synthesized from 1-[4-(4-azido-2-fluoro-phenyl)-piperazin-1-yl]-2-dimethylamino-ethanone (100 mg, 0.32 mmol), obtained in preparation 45, by following the procedure as described in example 1.

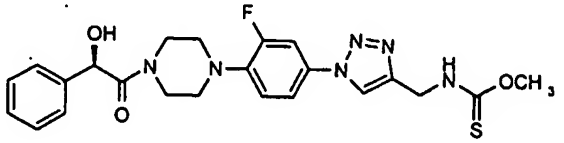
^{1}H NMR (200 MHz, $CDCl_3$): δ 8.04 and 7.81 (2s, 1H, rotamers in the ratio 4:1), 7.53-7.43 (m, 2H), 7.01(t, J=8.7 Hz, 2H), 4.89 and 4.64 (2d, J= 5.9 Hz, 2H, rotamers in the ratio 4:1), 4.19 and 4.01(2s, 3H, rotamers in the ratio 1:4), 3.89 - 3.78 (m, 4H), 3.26-3.09 (m, 6H), 2.30 (s, 6 H).

IR (KBr): 3448, 3194, 3136, 2942, 1640, 1522, 1455, 1229, 1147, 1049, 1018, 863 cm^{-1}

ES-MS (m/e): 458 (M^++23), 436.3 (M^++1).

Example 101:

(1-{3-Fluoro-4-[4-(2(R)-hydroxy-2-phenyl-acetyl)-piperazin-1-yl]-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



The title compound (70 mg, 59 %) was synthesized from 1-[4-(4-azido-2-difluoro-phenyl)- piperazin-1-yl]-2-hydroxy-2-phenyl-ethanone (87 mg, 0.25 mmol), obtained from preparation 46, by following the procedure as described in example 1.

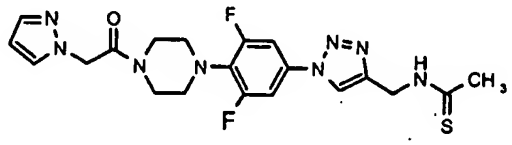
^{1}H NMR (200MHz, $CDCl_3$): δ 8.02 and 7.78 (2s, 1H, rotamers in the ratio 4:1), 7.48 – 7.25 (m, 8H), 7.00 – 6.82 (m, 2H), 5.29 (d, J = 6.2 Hz, 1H), 4.89 and 4.76 (2d, J = 5.8 Hz, 2H, rotamers in the ratio 4:1), 4.01 and 3.99 (2s, 3H, rotamers in the ratio 1:4), 3.85 – 3.60 (m, 2H), 3.61 – 3.30 (m, 2H), 3.12 – 2.84 (m, 4H).

IR (Neat): 3263, 3009, 2946, 1644, 1520, 1448, 1388, 1242, 1025, 756 cm^{-1}.

CI-MS (m/e): 485 (M^++1), 453.

Example 102:

(1-{3,5-Difluoro-4-[4-(2-pyrazol-1-yl-acetyl)-piperazin-1-yl]-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



The title compound (65 mg, 34 %) was synthesized from 1-[4-(4-azido-2,6-difluoro-phenyl)- piperazin-1-yl]-2-pyrazol-1-yl-ethanone (140 mg, 0.40 mmol), obtained in preparation 48, following the same procedure as described in example 1.

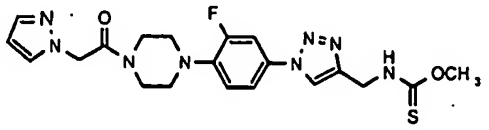
^{1}H NMR (200MHz, $CDCl_3$): δ 8.04 and 7.80 (2s, 1H, rotamers in the ratio 4:1), 7.54 (s, 2H), 7.29 (d, J= 9.3 Hz, 2H), 6.93 (bs, 1H), 6.34 (s, 1H), 5.06 (s, 2H), 4.89 and 4.64 (2d, J = 5.9 Hz, 2H, rotamers in the ratio 4:1), 4.09 and 3.99 (2s, 3H, rotamers in the ratio 1:5), 3.82 – 3.62 (m, 4H), 3.28 – 3.08 (m, 4H).

IR (KBr): 3435, 2926, 1668, 1517, 1456, 1225, 1199, 1146, 1033, 854, 753 cm^{-1}.

CI-MS (m/e): 445 (M^+-31), 413, 388

Example 103:

(1-{3-Fluoro-4-[4-(2-pyrazol-1-yl-acetyl)-piperazin-1-yl]-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



The title compound (150 mg, 67 %) was synthesized from 1-[4-(4-azido-2-fluoro-phenyl)-piperazin-1-yl]-2-pyrazol-1-yl-ethanone (160 mg, 0.49 mmol), obtained in preparation 49, following the same procedure as described in example 1.

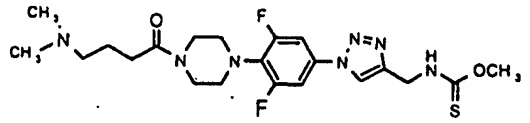
^{1}H NMR (200MHz, $CDCl_3$): δ 8.09 and 7.82 (2s, 1H, rotamers in the ratio 5:1), 7.62 – 7.50 (m, 2H), 7.50 – 7.30 (m, 2H), 7.10 – 7.05 (m, 1H), 6.98 (t, J = 8.9 Hz, 1H), 6.38 – 6.22 (m, 1H), 5.10 (s, 2H), 4.91 and 4.68 (2d, J = 5.8 Hz, 2H, rotamers in the ratio 5:1), 4.14 and 4.10 (2s, 3H, rotamers in the ratio 1:3), 3.94 – 3.64 (m, 4H), 3.19 – 3.02 (m, 4H).

IR (KBr): 3241, 2944, 1660, 1519, 1238, 1149, 1032, 869, 754 cm^{-1}.

CI-MS (m/e): 427 (M^+-31)

Example 104:

(1-{4-[4-(4-Dimethylamino-butyryl)- piperazin-1-yl]-3,5-difluoro-phenyl }-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



The title compound (200 mg, 35 %) was synthesized from 4-dimethylamino-butyric acid (157 mg, 1.19 mmol) and [1-(3,5-difluoro-4-piperazin-1-yl-phenyl)-1H-[1,2,3] triazol-4-ylmethyl]-thiocarbamic acid O-methyl ester, obtained in example 6, by following the procedure as described in example 27.

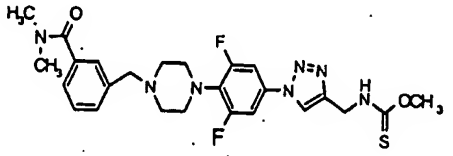
^{1}H NMR (200 MHz, DMSO): δ 9.71 (bs, 1H), 8.76 and 8.72 (2s, 1H, rotamers in the ratio 3:1), 7.79 (d, J = 9.8 Hz, 2H), 4.79 and 4.59 (2d, J = 5.7 Hz, 2H, rotamers in the ratio 4:1), 3.99 and 3.92 (2s, 3H, rotamers in the ratio 1:5), 3.76 – 3.56 (m, 4H), 3.54 – 3.30 (m, 4H), 2.50 – 2.30 (m, 4H), 2.25 (s, 6H).

IR (KBr): 2930, 1634, 1519, 1453, 1214, 1147, 1032, 855, 758 cm^{-1}.

CI-MS (m/e): 482 (M^++1), 450

Example 105:

(1-{4-[4-(3-Dimethylcarbamoyl-benzyl)-piperazin-1-yl]-3,5-difluoro-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)- thiocarbamic acid O-methyl ester



The title compound (150 mg, 29 %) was synthesized from 3-[4-(4-azido-2,6-difluoro-phenyl)- piperazin-1-ylmethyl]-N,N-dimethyl- benzamide (400 mg, 1.0 mmol) obtained in preparation 51, by following the procedure as described in example 1.

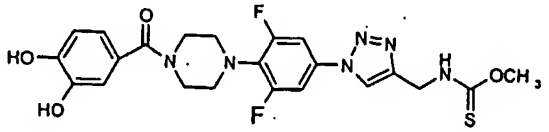
^{1}H NMR (400MHz, $CDCl_3$): δ 8.04 and 7.78 (2s, 1H, rotamers in the ratio 5:1), 7.46 – 7.28 (m, 6H), 6.89 – 6.81 (m, 1H), 4.89 and 4.64 (2d, J = 5.9 Hz, 2H, rotamers in the ratio 5 :1), 4.12 and 3.99 (2s, 3H, rotamers in the ratio 1:6), 3.58 (s, 2H), 3.34 – 3.22 (m, 4H), 3.12 (s, 3H), 2.99 (s, 3H), 2.64 – 2.52 (m, 4H).

IR (KBr): 3221, 2940, 1626, 1517, 1455, 1396, 1204, 1140, 1038, 858, 753 cm^{-1}.

CI-MS (m/e): 530 (M^++1), 498

Example 106:

(1-{4-[4-(3,4-Dihydroxy-benzoyl)-piperazin-1-yl]-3,5-difluoro-phenyl}-1H-1,2,3]triazol-ylmethyl)-thiocarbamic acid O-methyl ester



The title compound (50 mg, 12 %) was synthesized from 3,4-dihydroxy-benzoic acid (151 mg, 0.99 mmol) and [1-(3,5-difluoro-4-piperazin-1-yl-phenyl)-1H-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid O-methyl ester, obtained in example 6, by following the procedure as described in example 27.

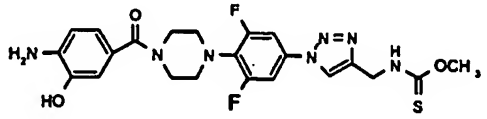
^{1}H NMR (400MHz, DMSO): δ 9.68-9.58 (m, 1H), 9.28 (s, 1H), 9.16 (s,1H), 8.72 and 8.67 (2s, 1H, rotamers in the ratio 3:1), 7.76 (d, J=10.2 Hz, 2H), 6.84 (s, 1H), 6.80-6.74 (m, 2H), 4.72 and 4.43 (2d, , J = 5.6 Hz, 2H, rotamers in the ratio 3:1), 3.94 and 3.88 (2s, 3H, rotamers in the ratio 1:4), 3.66-3.54 (m, 4H), 3.24 - 3.12 (m, 4H).

IR (KBr): 3268, 1596, 1517, 1442, 1288, 1227, 1148, 1025, 851 cm^{-1}.

ES-MS (m/e): 527 (M^++23), 505 (M^++1).

Example 107:

(1-{4-[4-(4-Amino-3-hydroxy-benzoyl)-piperazin-1-yl]-3,5-difluoro-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



The title compound (100 mg, 18 %) was synthesized from 4-amino-3-hydroxy-benzoic acid (200 mg, 1.30 mmol) and [1-(3,5-difluoro-4-piperazin-1-yl-phenyl)-1H-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid O-methyl ester, obtained in example 6, by following the procedure as described in example 27.

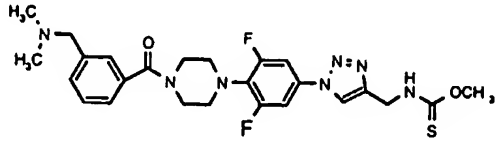
^{1}H NMR (400MHz, DMSO): δ 9.66 – 9.60 (m, 1H), 9.24 (bs, 1H), 8.72 and 8.70 (2s, 1H, rotamers in the ratio 3:1), 7.75 (d, J = 9.9 Hz, 2H), 6.79 (s, 1H), 6.78 – 6.70 (m, 1H), 6.58 (d, J = 7.8 Hz, 1H), 4.92 (bs, 2H), 4.73 and 4.24 (2d, J = 5.6 Hz, 2H, rotamers in the ratio 3:1), 3.95 and 3.88 (2s, 3H, rotamers in the ratio 1:3), 3.66 – 3.54 (m, 4H), 3.24 – 3.09 (m, 4H).

IR (KBr): 3373, 1612, 1518, 1440, 1289, 1230, 1148, 1023, 854, 564 cm^{-1}.

ES-MS (m/e): 526 (M^++23), 504 (M^++1)

Example 108:

(1-{4-[4-(3-Dimethylaminomethyl-benzoyl)-piperazin-1-yl]-3,5-difluoro- phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



The title compound (40 mg, 12 %) was synthesized from [4-(4-azido-2,6-difluoro-phenyl)-piperazin-1-yl]-(3-dimethylaminomethyl-phenyl)-methanone (250 mg, 0.63 mmol), obtained in preparation 53, by following the procedure as described in example 1.

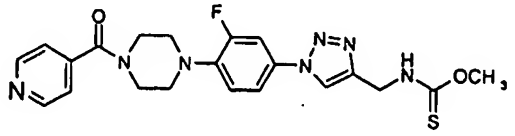
^{1}H NMR (200MHz, $CDCl_3$): δ 8.04 and 7.82 (2s, 1H, rotamers in the ratio 4:1), 7.54 – 7.18 (m, 6H), 7.00 – 6.82 (m, 1H), 4.89 and 4.68 (2d, J = 5.6 Hz, 2H, rotamers in the ratio 4:1), 4.16 and 3.99 (2s, 3H, rotamers in the ratio 1:6), 3.78 – 3.39 (m, 4H), 3.54 (s, 2H), 3.36 – 3.08 (m, 4H), 2.28 (s, 6H).

IR (KBr): 3422, 2924, 1628, 1517, 1458, 1201, 1024, 850, 700 cm^{-1}.

CI-MS (m/e): 530 (M^++1), 498

Example 109:

(1-{3-Fluoro-4-[4-(pyridine-4-carbonyl)-piperazin-1-yl]-phenyl}-1H-[1, 2, 3] triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



The title compound (66 mg, 36 %) was synthesized from [4-(4-azido-2-fluoro-phenyl)-piperazin-1-yl]-pyridin-4-yl-methanone (133 mg, 0.41 mmol), obtained in preparation 54, using the same procedure as described in example 1.

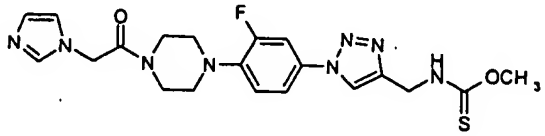
^{1}H NMR (200MHz, $CDCl_3$): δ 8.69 (d, J = 5.6 Hz, 2H), 8.04 and 7.82 (2s, 1H, rotamers in the ratio 4:1), 7.59 – 7.39 (m, 2H), 7.32 (d, J = 5.9 Hz, 2H), 7.19 – 6.98 (m, 1H), 6.97 – 6.88 (m, 1H), 4.91 and 4.64 (2d, J = 5.9 Hz, 2H, rotamers in the ratio 4:1), 4.18 and 4.02 (2s, 3H, rotamers in the ratio 1:4), 4.11 – 3.84 (m, 2H), 3.62 – 3.49 (m, 2H), 3.30 – 3.01 (m, 4H).

IR (KBr): 3431, 2924, 1635, 1520, 1440, 1243, 1149, 1016, 756 cm^{-1}.

CI-MS (m/e): 456 (M^++1), 424

Example 110:

(1-{3-Fluoro-4-[4-(2-imidazol-1-yl-acetyl)-piperazin-1-yl]-phenyl} -1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



The title compound (26 mg, 26 %) was synthesized from 1-[4-(4-azido-2-fluoro-phenyl)-piperazin-1-yl]-2-imidazol-1-yl-ethanone (72 mg, 0.22 mmol), obtained in preparation 55, by using the same procedure as described in example 1.

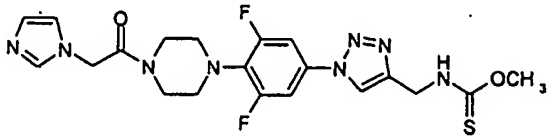
^{1}H NMR (200 MHz, $CDCl_3$): δ 8.06 and 7.81 (2s, 1H, rotamers in the ratio 4:1), 7.64 – 7.45 (m, 1H), 7.42 – 7.38 (m, 2H), 7.19 – 6.82 (m, 2H), 6.81 – 6.68 (m, 1H), 4.91 and 4.65 (2d, J = 5.9 Hz, 2H, rotamers in the ratio 5:1), 4.85 (s, 2H), 4.61 and 4.01 (2s, 3H, rotamers in the ratio 1:5), 3.89 – 3.78 (m, 2H), 3.74 – 3.49 (m, 2H), 3.20 – 3.09 (m, 4H).

IR (KBr): 3422, 2925, 1656, 1518, 1234, 1148, 1033, 866 cm^{-1}.

ES-MS (m/e): 481 (M^++23), 459 (M^++1)

Example 111:

(1-{3,5-Difluoro-4-[4-(2-imidazol-1-yl-acetyl)-piperazin-1-yl]-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



The title compound (75 mg, 8%) was synthesized from 1-[4-(4-azido-2-fluoro-phenyl)- piperazin-1-yl]-2-imidazol-1-yl-ethanone (660 mg, 1.90 mmol), obtained in preparation 56, following the same procedure as described in example 1.

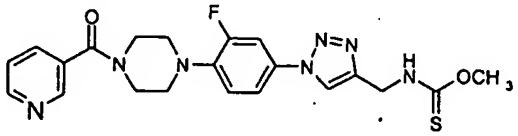
^{1}H NMR (200MHz, $CDCl_3$): δ 8.09 (s, 1H), 7.58 (s, 1H), 7.39 – 7.29 (m, 2H), 7.19 – 7.09 (m, 1H), 7.03 – 6.94 (m, 1H), 4.94 (d, J = 5.8 Hz, 2H), 4.84 (s, 2H), 4.12 and 4.01 (2s, 3H, rotamers in the ratio 1:5), 3.92 – 3.74 (m, 2H), 3.68 – 3.54 (m, 2H), 3.36 – 3.18 (m, 4H).

IR (KBr): 3426, 1653, 1517, 1427, 1233, 1154, 1032, 857, 756, 663 cm^{-1}.

CI-MS (m/e): 477 (M^++1), 455

Example 112:

(1-{3-Fluoro-4-[4-(pyridine-3-carbonyl)-piperazin-1-yl]-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



The title compound (40 mg, 16 %) was synthesized from [4-(4-azido-2-fluoro-phenyl)-piperazin-1-yl]-pyridin-4-yl-methanone (178 mg, 0.55 mmol), obtained in preparation 57, by following the procedure as described in example 1.

^{1}H NMR (200 MHz, $CDCl_3$): δ 8.77 – 8.64 (m, 2H), 8.05 (s, 1H), 7.84 – 7.74 (m, 1H), 7.58 – 7.38 (m, 3H), 7.03 (t, J = 8.9 Hz, 1H), 7.00 – 6.90 (m, 1H), 4.91 and 4.65 (2d, J = 5.9 Hz, 2H, rotamers in the ratio 5:1), 4.08 and 3.99 (2s, 3H, rotamers in the ratio 1:5), 4.32 – 3.48 (m, 4H), 3.32 – 3.04 (m, 4H).

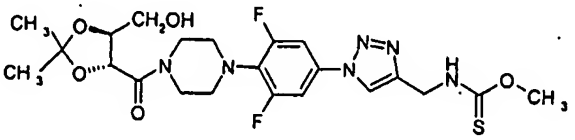
CI-MS (m/e): 424 (M^+-31), 367

IR (KBr): 3424, 2927, 1649, 1529, 1438, 1243, 1149, 1011, 864, 810 cm^{-1}.

CI-MS (m/e): 424 (M^+-31), 367

Example 113:

(1-{3,5-Difluoro-4-[4-(5(S)-hydroxymethyl-2,2-dimethyl-[1,3]dioxolane-4(R)-carbonyl)piperazin-1-yl]phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamicacid O-methyl ester



The title compound (100 mg, 25%) was synthesized from [4-(4-azido-2,6-difluoro-phenyl)-piperazin-1-yl]-(5-hydroxymethyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-methanone (300 mg, 0.75 mmol), obtained in preparation 59, by following the procedure as described in example 1.

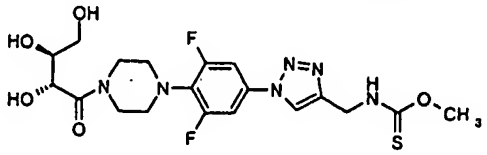
^{1}H NMR (DMSO, 400 MHz): δ 8.04 and 7.81 (2s, 1H, rotamers in the ratio 4:1), 7.31 (d, J = 9.4 Hz, 2H), 6.86 – 6.81 (m, 1H), 4.90 and 4.65 (2d, J = 6.1 Hz, 2H, rotamers in the ratio 5:1), 4.74 – 4.69 (m, 2H), 4.55 (d, J = 7.5 Hz, 1H), 4.11 and 4.00 (2s, 3H, rotamers in the ratio 1:6), 3.96 – 3.82 (m, 2H), 3.77 – 3.65 (m, 4H), 3.25 – 3.19 (m, 4H), 1.47 (s, 3H), 1.42 (s, 3H).

IR (Neat): 3374, 2928, 1640, 1518, 1448, 1384, 1210, 1153, 1038, 856 cm^{-1}.

ES-MS (m/e): 549 (M^+ + 23), 527 (M^+ + 1)

Example 114:

(1-{3,5-Difluoro-4-[4-(2(R),3(S),4-trihydroxy-butyryl)-piperazin-1-yl]-phenyl}-1H [1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



(1-{3,5-Difluoro-4-[4-(5(S)-hydroxymethyl-2,2-dimethyl-[1,3]dioxolane-4(R)-carbonyl)piperazin-1-yl]phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamicacid-O-methyl ester (350 mg, 0.66 mmol), obtained in example 113, was dissolved in 60 % TFA in DCM (10 mL) at 0 °C. The reaction mixture was stirred for 2 to 3 hours at 25-35 °C.

The solvent was removed under vacuum and the reaction mixture was co-evaporated with toluene (2 x 10 mL) and the residue was purified by preparative thin layer chromatography (TLC) to yield the title compound (80 mg, 25%).

^{1}H NMR (DMSO, 400 MHz): δ 9.67 – 9.59 (m, 1H), 8.71 and 8.67 (2s, 1H, rotamers in

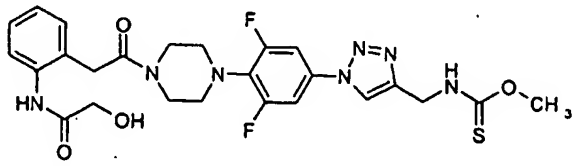
the ratio 4:1), 7.75 (d, J = 9.9 Hz, 2H), 4.73 (d, J = 5.6 Hz, 1H), 4.62 – 4.58 (m, 2H), 4.46 – 4.44 (m, 2H), 3.94 and 3.88 (2s, 3H, rotamers in the ratio 1:4), 3.67 – 3.59 (m, 5H), 3.49 – 3.42 (m, 1H), 3.36 – 3.31 (m, 1H), 3.23 – 3.11 (m, 5H).

IR (Neat):3353, 2926, 1633, 1518, 1453, 1390, 1330, 1276, 1229, 1120, 1029, 857, 757 cm^{-1}.

ES-MS (m/e): 509 (M^+ + 23), 487 (M^+ + 1)

Example 115:

{1-[3,5-Difluoro-4-(4-{2-[2-(2-hydroxy-acetylamino)-phenyl]-acetyl}-piperazin-1-yl)-phenyl]-1H-[1,2,3]triazol-4-ylmethyl}-thiocarbamic acid O-methyl ester



The title compound (200 mg, 38 %) was synthesized from N-(2-{2-[4-(4-azido-2,6-difluoro-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-phenyl)-2-hydroxy-acetamide (400 mg, 0.93 mmol), obtained in preparation 62, by following the procedure as described in example 1.

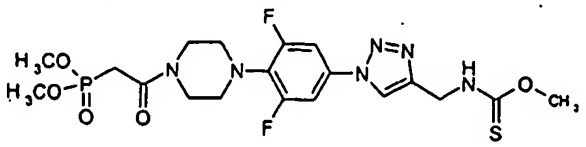
^{1}H NMR (DMSO, 400 MHz): δ 9.71 (s, 1H), 9.68 – 9.61 (m, 1H), 8.71 and 8.67 (2s, 1H, rotamers in the ratio 3:1), 7.70 (d, J = 10.2 Hz, 2H), 7.68 (d, J = 8.0 Hz, 1H), 7.30 – 7.23 (m, 2H), 7.10 (dt, J_1 = 1.2 Hz, J_2 = 7.2 Hz, 1H), 5.79 (t, J=5.9 Hz, 1H), 4.70 and 4.43 (2d, J = 5.6 Hz, 2H, rotamers in the ratio 3:1), 3.99 (d, J = 5.9 Hz, 2H), 3.94 and 3.88 (2s, 3H, rotamers in the ratio 1:3), 3.77 (s, 2H), 3.76 – 3.68 (m, 2H), 3.67 – 3.58 (m, 2H), 3.21 – 3.15 (m, 2H), 3.15 – 3.08 (m, 2H).

IR (KBr): 3420, 1631, 1520, 1456, 1228, 1153, 1036, 856, 758, 491 cm^{-1}.

CI-MS (m/e): 560 (M^++1), 528 (M^+-31).

Example 116:

[2-(4-{2,6-Difluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazin-1-yl)-2-oxo-ethyl]-phosphonic acid dimethyl ester



The title compound (180 mg, 64 %) was synthesized from (dimethoxy-phosphoryl)-acetic acid (136 mg, 0.82 mmol) and 1-(3,5-difluoro-4-piperazin-1-yl-phenyl)-1H-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid O-methyl ester, obtained in example 6, by following the procedure as described in example 27.

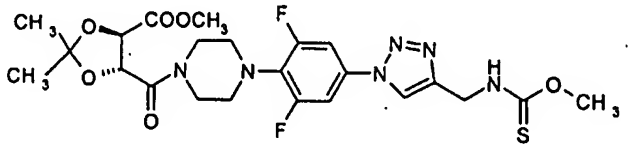
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.05 and 7.81 (2s, 1H, rotamers in the ratio 4:1), 7.30 (d, J = 9.4 Hz, 2H), 6.98 – 6.86 (m, 1H), 4.90 and 4.65 (2d, J = 5.9 Hz, 2H, rotamers in the ratio 4:1), 4.11 and 3.99 (2s, 3H, rotamers in the ratio 1:4), 3.86 (s, 2H), 3.80 (s, 3H), 3.78 – 3.65 (m, 4H), 3.38 – 3.19 (m, 4H), 3.13 (d, J = 22.0 Hz, 2H).

IR (KBr): 3227, 2924, 1638, 1517, 1457, 1368, 1250, 1209, 1148, 1031, 982, 850, 809, 566 cm^{-1}.

ES-MS (m/e): 519.2

Example 117:

5(R)-(4-{2,6-Difluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazine-1-carbonyl)-2,2-dimethyl-[1,3]dioxolane-4(R)-carboxylic acid methyl ester



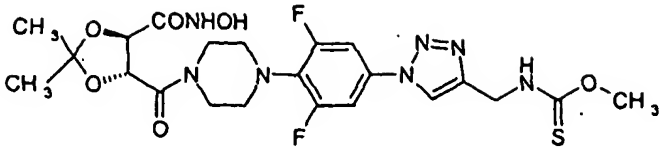
The title compound (300 mg, 38 %) was synthesized from 5-[4-(4-azido-2,6-difluoro-phenyl)-piperazine-1-carbonyl]-2,2-dimethyl-[1,3]dioxolane-4-carboxylic acid methyl ester (600 mg, 1.41 mmol), by following the procedure as described in example 1

^{1}H NMR ($CDCl_3$,200 MHz): δ 8.06 and 7.84 (2s, 1H, rotamers in the ratio 4:1), 7.31 (d, J = 9.1 Hz, 2H), 7.12 – 6.92 (m, 1H), 5.39 (d, J = 5.3 Hz, 1H), 4.90 (t, J = 5.9 Hz, 3H), 4.64 (rotameric doublet, J = 6.0 Hz), 4.11 and 3.99 (2s, 3H, rotamers in the ratio 1:4), 3.81 (s, 3H), 4.00 – 3.56 (m, 4H), 3.39 – 3.30 (m, 4H), 1.50 (s, 1H), 1.45 (s, 3H)

CI-MS (m/e): 555(M^++1), 522

Example 118:

(1-{3,5-Difluoro-4-[4-(5(R)-hydroxycarbamoyl-2,2-dimethyl-[1,3]dioxolane-4(R)-carbonyl)-piperazin-1-yl]-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



NaOH (3.8 M in methanol, 2.7 mL) was added to hydroxylamine hydrochloride (1.6 M in methanol, 4 mL) at 0 °C and stirred for 2 hours. This hydroxylamine solution was added to a stirred solution of 5-(4-{2,6-difluoro-4-[4-methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazine-1-carbonyl)-2,2-dimethyl-[1,3]dioxolane-4-carboxylic acid methyl ester (500 mg, 0.9 mmol), obtained in example 117, in methanol at 0 °C by filtration. The reaction mixture was stirred at 25-35 °C for 45 minutes. The solvent was removed and the residue was purified by column chromatography (0.02:1 methanol/chloroform) to furnish the title compound (180 mg, 36%).

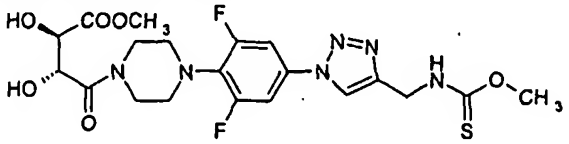
^{1}H NMR (DMSO, 200 MHz): δ 10.91 (s, 1H), 9.78 – 9.58 (m, 1H), 9.01 (s, 1H), 8.73 and 8.68 (2s, 1H, rotamers in the ratio 3:1), 7.76 (d, J = 9.9 Hz, 2H), 5.01 (d, J = 5.6 Hz, 1H), 4.83 (d, J = 5.6 Hz, 1H), 4.72 and 4.44 (2d, J = 5.6 Hz, 2H, rotamers in the ratio 4:1), 3.94 and 3.88 (2s, 3H, rotamers in the ratio 1:3), 3.74 – 3.52 (m, 4H), 3.22 – 3.00 (m, 4H), 1.42 (s, 3H), 1.34 (s, 3H).

IR (Neat): 3262, 2927, 1644, 1617, 1447, 1383, 1211, 1149, 1033, 859, 755, 616 cm^{-1}.

ES-MS (m/e): 578 (M^+ + 23), 556 (M^+ +1)

Example 119:

4-(4-{2,6-Difluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazin-1-yl)- 2(R),3(R) -dihydroxy-4-oxo-butyric acid methyl ester



Using the same procedure as described in example 114, the title product (90 mg, 32 %) was synthesized from 5-(4-{2,6-difluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazine-1-carbonyl)-2,2-dimethyl-[1,3]dioxolane-4-carboxylic acid methyl ester (300 mg, 0.54 mmol), obtained in example 117.

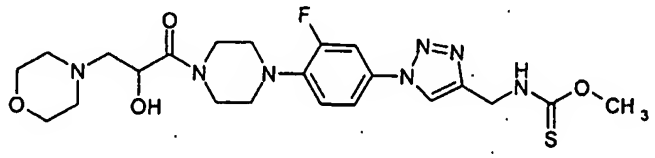
^{1}H NMR ($CDCl_3$,400 MHz): δ 8.05and 7.80 (2s, 1H, rotamers in the ratio 4 :1), 7.32 (d, J=9.4 Hz, 2H), 6.91-6.84 (m, 1H), 4.90 and 4.65(2d, J=6.1 Hz, 2H, rotamers in the ratio 4:1), 4.78 (d, J=1.8 Hz, 1H), 4.69 (d, J=1.6Hz, 1H), 4.11 and 4.00 (2s, 3H, rotamers in the ratio 1:3), 3.88 (s, 3H), 3.79-3.62 (m, 4H),3.35-3.22 (m, 4H).

IR (Neat): 3266, 2928, 1642, 1518, 1447, 1384 cm^{-1}.

CI-MS (m/e): 514(M^+), 486, 396

Example 120:

(1-{3-Fluoro-4-[4-(2-hydroxy-3-morpholin-4-yl-propionyl)-piperazin-1-y l]-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



The title compound (13 mg, 13%) was prepared from 1-[4-(4-azido-2-fluoro-phenyl)-piperazin-1-yl]-2-hydroxy-3-morpholin-4-yl-propan-1-one (75 mg, 0.2 mmol), obtained in preparation 65, by following the same procedure as described in example 1.

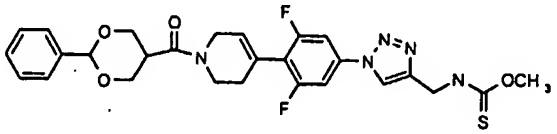
^1H NMR ($CDCl_3$,400 MHz): δ 8.04 and 7.81 (2s, 1H, rotamers in the ratio 3:1), 7.51 (dd, J_1 = 2.6, J_2 = 12.6 Hz, 1H), 7.48 – 7.39 (m, 1H), 7.03 (t, J = 8.8 Hz, 1H), 6.94 – 6.84 (m, 1H), 4.91 and 4.65 (2d, J = 5.9 Hz, 2H, rotamers in the ratio 4:1), 4.58 – 4.49 (m, 1H), 4.11 and 4.00 (2s, 3H, rotamers in the ratio 1:4), 3.99 – 3.86 (m, 1H), 3.84 – 3.62 (m, 8H), 3.26 – 3.08 (m, 4H), 2.78 – 2.51 (m, 6H).

IR (Neat): 3254, 2924, 2854, 1640, 1520, 1453, 1388, 1235, 1116, 1027, 1008, 984, 867, 757,667, 618 cm^{-1}.

ES-MS (m/e): 508 (M^+ + 1).

Example 121:

(1-{3,5-Difluoro-4-[1-(2-phenyl-[1,3]dioxane-5-carbonyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



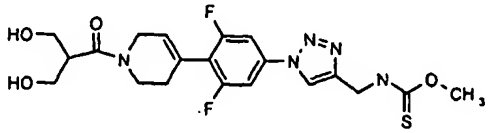
The title compound (42 mg, 36%) was synthesized from [4-(4-azido-2,6-difluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-(2-phenyl-[1,3]dioxan-5-yl)-methanone (90 mg, 0.21 mmol) obtained in preparation 66, by following the procedure as described in example 1.

^1H NMR (DMSO, 400 MHz): δ 9.66 (t, J = 5.9 Hz, 1H), 8.80 and 8.75 (2s, 1H, rotamers in the ratio 3:1), 7.83 (d, J = 8.5 Hz, 2H), 7.48 – 7.41 (m, 2H), 7.41 – 7.34 (m, 3H), 6.04 –

5.97 (m, 1H), 5.57 (s, 1H), 4.74 and 4.45 (2d, J = 5.6 Hz, 2H, rotamers in the ratio 4:1), 4.41 – 4.36 and 4.15 – 4.09 (2m, 2H), 4.27 (dd, J_1 = 4.5 Hz, J_2 = 11.5 Hz, 2H), 4.09 – 4.00 (m, 2H), 3.95 and 3.89 (2s, 3H, rotamers in the ratio 1:4), 3.84 – 3.77 and 3.72 – 3.65 (2m, 2H), 3.50 – 3.32 (m, 1H), 2.54 – 2.44 (m, 1H), 2.39 – 2.32 (m, 1H).
ES-MS (m/z): 556 (M^++1)

Example 122:

(1-{3,5-Difluoro-4-[1-(3-hydroxy-2-hydroxymethyl-propionyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester

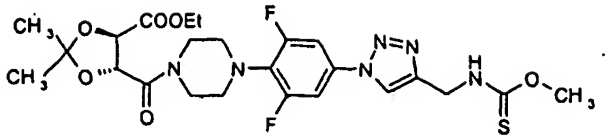


To a solution of (1-{3,5-difluoro-4-[1-(2-phenyl-[1,3]dioxane-5-carbonyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester (40 mg, 0.07 mmol), obtained in example 121, in tetrahydrofuran (THF) (3 mL), HCl (3N, 0.2 mL) was added and the solution was stirred for 24 hours at 25-35 °C.

The reaction mixture coevaporated with toluene (2 x 5 mL) under reduced pressure. The residue was purified by column chromatography (4:6 methanol/ chloroform) to afford the desired product (20 mg, 59 %).
^{1}H NMR (DMSO, 400 MHz): δ 9.66 (t, J = 5.9 Hz, 1H), 8.79 and 8.75 (2s, 1H, rotamers in the ratio 3:1), 7.82 (dd. J_1 = 4.8 Hz, J_2 = 13.4 Hz, 2H), 6.04 – 5.95 (m, 1H), 4.74 and 4.45 (2d, J = 5.6 Hz, 2H, rotamers in the ratio 4:1), 4.66 – 4.55 (m, 2H), 4.35 – 4.28 and 4.21 – 4.13 (2m, 2H), 3.95 and 3.89 (2s, 3H, rotamers in the ratio 1:4), 3.82 – 3.69 (m, 2H), 3.61 – 3.48 (m, 4H), 3.18 – 3.02 (m, 1H), 2.52 – 2.33 (m, 2H).
IR (KBr): 3384, 2940, 1618, 1511, 1453, 1364, 1203, 1148, 1033, 859, 756 cm^{-1}.
CI-MS (m/e): 467 (M^+), 432 (M^+-32), 387

Example 123:

5-(R) -(4-{2,6-Difluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazine-1-carbonyl)-2,2-dimethyl-[1,3]dioxolane-4(R)-carboxylic acid ethyl ester



The title compound (160 mg, 37 %) was synthesized from 2,2-dimethyl-[1,3]dioxolane-4,5-dicarboxylic acid monoethyl ester (254 mg, 1.23 mmol) and [1-(3,5-difluoro-4-piperazin-1-yl-phenyl)-1H-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid O-methyl ester obtained in example 6, by following the same procedure as described in example 27.

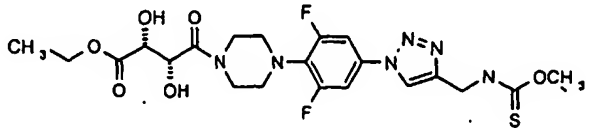
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 and 7.81 (2s, 1H, rotamers in the ratio 8:1), 7.31 (d. J = 9.1 Hz, 2H), 6.97 (t, J = 5.6 Hz, 1H), 5.36 (d, J = 6.1 Hz, 1H), 4.94 (d, J = 5.1 Hz, 1H), 4.90 and 4.65 (2d, J = 5.9 Hz, 2H, rotamers in the ratio 7:1), 4.30 – 4.23 (m, 2H), 4.11 and 3.99 (2s, 3H, rotamers in the ratio 1:9), 3.97 – 3.88 (m, 2H), 3.75 – 3.64 (m, 2H), 3.33 – 3.18 (m, 4H), 1.50 (s, 3H), 1.45 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H).

IR (KBr): 3251, 1754, 1636, 1517, 1466, 1366, 1254, 1211, 1148, 1114, 1038, 982, 855, 698 cm^{-1}.

ES-MS (m/e): 569.3 (M^++1).

Example 124:

4-(4-{2,6-Difluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazin-1-yl)-2(R), 3(R) - dihydroxy-4-oxo-butyric acid ethyl ester



By following the procedure as described in example 114, the title compound (60 mg, 40 %) was obtained from 5-(R)-(4-{2,6-difluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazine-1-carbonyl)-2,2-dimethyl-[1,3]dioxolane-4(R)-carboxylic acid ethyl ester (150 mg, 0.29 mmol) obtained in example 123.

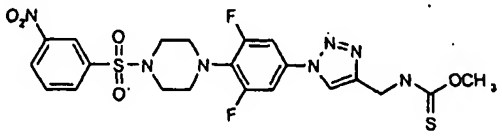
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.06 and 7.83 (2s, 1H, rotamers in the ratio of 5:1), 7.32 (d, J = 9.2 Hz, 2H), 7.06 – 6.90 (m, 1H), 4.91 and 4.65 (2d, J = 5.8 Hz, 2H, rotamers in the ratio 4:1), 4.81 (s, 1H), 4.50 – 4.24 (m, 3H), 4.11 and 3.99 (2s, 3H, rotamers in the ratio 1:5), 4.05 – 3.83 (m, 1H), 3.83 – 3.58 (m, 3H), 3.44 – 3.15 (m, 4H), 1.35 (t, J = 7.3 Hz, 3H).

IR (KBr): 3408, 2943, 1743, 1646, 1514, 1459, 1392, 1332, 1231, 1124, 1030, 838 cm^{-1}.

CI-MS (m/e): 529 (M^++1), 425, 369.

Example 125:

(1-{3,5-Difluoro-4-[4-(3-nitro-benzenesulfonyl)-piperazin-1-yl]-phenyl}-1H-[1,2,3] triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



To a stirred solution of [1-(3,5-difluoro-4-piperazin-1-yl-phenyl)-1H-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid O-methyl ester (120 mg, 0.54 mmol), obtained in example 6, in dry DCM at 0 °C was added triethylamine (0.15 mL, 1.08 mmol), 3-nitrobenzene sulphonyl chloride (120 mg, 0.54 mmol) and stirred at 25-35 °C for 9 to 13 hours. The reaction mixture was diluted with DCM and washed with water (2 x 10 mL), brine and dried over sodium sulphate. The organic layer was concentrated under vacuum and the residue was purified by column chromatography (0.7: 0.3 ethyl acetate/petroleum ether) to obtain the title product as a bright yellow solid (200 mg, 71%).

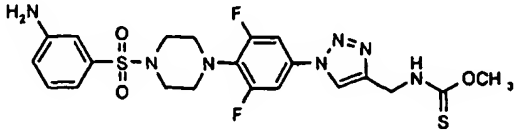
^{1}H NMR (DMSO, 400 MHz): δ 9.68 – 9.58 (m, 1H), 8.69 and 8.64 (2s, 1H, rotamers in the ratio 3:1), 8.57 (d, J = 8.3 Hz, 1H), 8.42 (t, J = 1.8 Hz, 1H), 8.23 (dd. J_1 = 1.6 Hz, J_2 = 7.7 Hz, 1H), 7.99 (t, J = 8.1 Hz, 1H), 7.72 (d, J = 10.0 Hz, 2H), 4.71 and 4.42 (2d, J = 5.9 Hz, 2H, rotamers in the ratio 4:1), 3.93 and 3.87 (2s, 3H, rotamers in the ratio 1:4), 3.38 – 3.19 (m, 4H), 3.19 – 3.04 (m, 4H).

IR (KBr): 3262, 2922, 1526, 1459, 1357, 1263, 1233, 1176, 1135, 1044, 950, 714, 575 cm^{-1}.

ES-MS (m/e): 554.3 (M^++1).

Example 126:

(1-{4-[4-(3-Amino-benzenesulfonyl)-piperazin-1-yl]-3,5-difluoro-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



To a suspension of tin chloride (563 mg, 2.34 mmol) in methanol (MeOH) (10 ml), Conc. HCl (2 mL) was added and the mixture was cooled to -10 °C . A solution of 1-

{3,5-difluoro-4-[4-(3-nitro-benzenesulfonyl)-piperazin-1-yl]-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester (130 mg, 0.25 mmol), obtained in example 125, in MeOH (5 mL) was transferred to the above mixture and the reaction mixture was stirred for over night at 25-35 °C. Reaction mixture was quenched with sodium bicarbonate solution (20%, 20 mL) and extracted with DCM (2 x 30 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The organic layer was concentrated under vacuum and the residue was purified by column chromatography (4:6 methanol/chloroform) to give the title product as light yellow solid (70 mg, 57%).

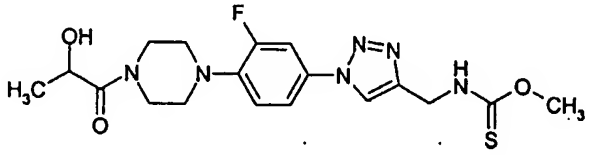
^{1}H NMR (DMSO, 400 MHz): δ 9.63 (t, J = 5.6 Hz, 1H), 8.69 and 8.65 (2s, 1H, rotamers in the ratio 4:1), 7.72 (d, J = 9.9 Hz, 2H), 7.27 (t, J = 7.7 Hz, 1H), 6.94 (t, J = 2.1 Hz, 1H), 6.90 – 6.82 (m, 2H), 5.66 (s, 2H), 4.71 and 4.42 (2d, J = 5.6 Hz, 2H, rotamers in the ratio 4:1), 3.93 and 3.98 (2s, 3H, rotamers in the ratio 1:4), 3.28 – 3.21 (m, 4H), 3.04 – 2.97 (m, 4H).

IR (KBr): 3375, 2855, 1518, 1453, 1317, 1270, 1231, 1207, 1158, 1043, 948, 859, 733, 580 cm^{-1}.

ES-MS (m/e): 524.3 (M^++1), 546.3 (M^++23).

Example 127:

(1-{3-Fluoro-4-[4-(2-hydroxy-propionyl)-piperazin-1-yl]-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



The title compound (50 mg, 45 %) was synthesized from 1-[4-(4-azido-2-fluoro-phenyl)-piperazin-1-yl]-2-hydroxy-propan-1-one (80 mg, 0.27 mmol), obtained in preparation 67, by following the procedure as described in example 1.

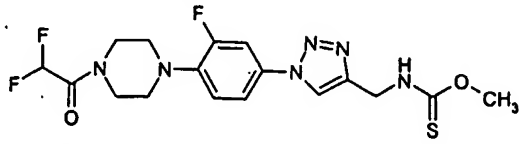
1H NMR ($CDCl_3$ & CD_3OD, 200 MHz): δ 8.14 and 7.89 (2s, 1H, rotamers in the ratio 5:1), 7.58 – 7.40 (m, 2H), 7.04 (t, J = 9.0 Hz, 1H), 4.86 and 4.63 (2s, 2H, rotamers in the ratio 5:1), 4.51 (q, J = 4.7 Hz, 1H), 4.10 and 3.99 (2s, 3H, rotamers in the ratio 1:5), 3.96 – 3.86 (m, 1H), 3.69 – 3.57 (m, 4H), 3.28 – 3.03 (m, 4H), 1.37 (d, J = 6.4 Hz, 3H).

IR (KBr): 3206, 2924, 1633, 1526, 1443, 1226, 1151, 1050, 1014, 981, 862, 769 cm^{-1}.

ES-MS (m/e): 445 (M^++23), 423 (M^++1)

Example 128:

(1-{4-[4-(2,2-Difluoro-acetyl)-piperazin-1-yl]-3-fluoro-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



The title compound (80 mg, 57 %) was synthesized from (1-{4-[4-(2, 2-difluoro-acetyl)-piperazin-1-yl]-3-fluoro-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester (100 mg, 0.33 mmol), obtained in preparation 68, by following the same procedure as described in example 1.

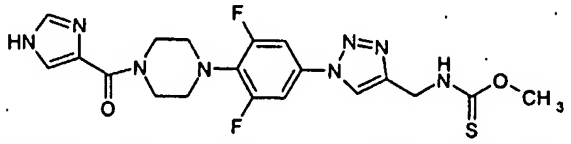
1H NMR ($CDCl_3$, 200 MHz): δ 8.06 and 7.82 (2s, 1H, rotamers in the ratio 5:1), 7.60 - 7.36 (m, 2H), 7.02 (t, J = 8.7 Hz, 1H), 7.02 – 6.90 (m, 1H), 6.15 (t, J = 53.6 Hz, 1H), 4.90 and 4.65 (2d, J = 5.9 Hz, 2H, rotamers in the ratio 5:1), 4.12 and 4.00 (2s, 3H, rotamers in the ratio 1:5), 3.92 – 3.76 (m, 4H), 3.26 – 3.10 (m, 4H).

IR (KBr): 3443, 3196, 2932, 1661, 1521, 1228, 1149, 1126, 1063, 978, 846, 725 cm^{-1}.

ES-MS (m/e): 451 (M^++23), 429 (M^++1)

Example 129:

(1-{3,5-Difluoro-4-[4-(1H-imidazole-4-carbonyl)-piperazin-1-yl]-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



The title compound (50 mg, 41 %) was synthesized from 1H-imidazole-4-carboxylic acid (60 mg, 0.54 mmol) and [1-(3,5-difluoro-4-piperazin-1-yl-phenyl)-1H-[1,2,3] triazol-4-yl-methyl]-thiocarbamic acid O-methyl ester, obtained in example 6, by following the procedure as described in example 27.

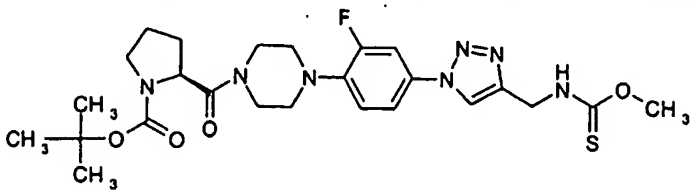
1H NMR (DMSO, 400 MHz): δ 12.57 – 12.39 (bs, 1H), 9.69 – 9.57 (m, 1H), 8.72 and 8.67 (2s, 1H, rotamers in the ratio 3:1), 7.82 – 7.70 (m, 4H), 4.72 and 4.43 (2d, J = 5.6 Hz, 2H, rotamers in the ratio 3:1), 3.95 and 3.89 (2s, 3H, rotamers in the ratio 1:3), 3.29 – 3.25 (m, 4H), 3.22 – 3.18 (m, 4H).

IR (KBr): 3421, 3219, 2922, 1601, 1517, 1441, 1274, 1198, 1029, 851, 757, 684 cm^{-1}.

ES-MS (m/e): 485 (M^++23), 463 (M^++1)

Example 130:

2(S)-(4-{2-Fluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazine-1-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester



The title compound (100 mg, 5 %) was synthesized from 2-[4-(4-azido-2-fluoro-phenyl)-piperazine-1-carbonyl]-pyrrolidine-1-carboxylic acid tert-butyl ester (1.3 grams, 3.11 mmol), obtained in preparation 69, by following the same procedure as described in example 1.

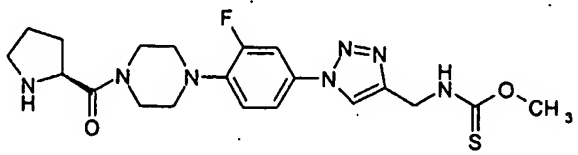
1H NMR (CDCl3, 200 MHz): δ 8.05 and 7.81 (2s, 1H, rotamers in the ratio 5:1), 7.56 – 7.34 (m, 2H), 7.08 – 6.86 (m, 2H), 4.90 (d, J = 5.9 Hz, 2H), 4.11 and 3.99 (2s, 3H, rotamers in the ratio 1:5), 3.92 – 3.36 (m, 6H), 3.28 – 3.00 (m, 4H), 2.24 – 1.63 (m, 4H), 1.47 (s, 9H).

IR (Neat): 3243, 2975, 1685, 1520, 1444, 1043, 1366, 1231, 1161, 1038, 865, 755 cm^{-1}.

ES-MS (m/e): 570 (M^++23), 548 (M^++1)

Example 131:

(1-{3-Fluoro-4-[4-(pyrrolidine-2(S)-carbonyl)-piperazin-1-yl]-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



The title compound (50 mg, 62 %) was synthesized from 2-(4-{2-fluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazine-1-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (100 mg, 0.18 mmol), obtained in example 130, by using trifluoroacitic acid at 25-35 °C

1H NMR (CDCl3, 200 MHz): δ 8.06 (s, 1H), 7.60 – 7.32 (m, 2H), 7.01 (t, J = 8.7 Hz, 1H), 4.91 (d, J = 5.1 Hz, 2H), 4.76 – 4.56 (m, 1H), 4.11 and 3.99 (2s, 3H, rotamers in the

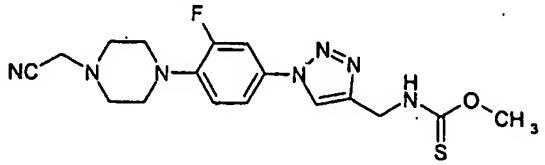
ratio 1:5), 3.84 – 3.54 (m, 4H), 3.40 – 3.28 (m, 4H), 3.27 – 3.04 (m, 3H), 2.22 – 1.76 (m, 4H).

IR (Neat): 3286, 1611. 1520, 1450, 1199, 1128, 1052, 865, 757, 720 cm^{-1}.

ES-MS (m/e): 470 (M^++23), 448 (M^++1)

Example 132:

{1-[4-(4-Cyanomethyl-piperazin-1-yl)-3-fluoro-phenyl]-1H-[1,2,3]triazol-4-ylmethyl}-thiocarbamic acid O-methyl ester



The title compound (20 mg, 9 %) was synthesized from [4-(4-Azido-2-fluoro-phenyl)-piperazin-1-yl]-acetonitrile (150 mg, 0.58 mmol), obtained in preparation 70, by using the same procedure as described in example 1.

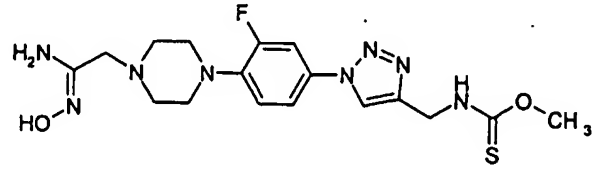
^{1}H NMR (200 MHz, $CDCl_3$) : δ 8.03 and 7.81 (2s, 1H, rotamers in the ratio 3:1), 7.51 – 7.26 (m, 2H), 7.02 (t, J = 8.7 Hz, 1H), 7.00 – 6.92 (m, 1H), 4.90 and 4.65 (2d, J = 6.0 Hz, 2H, rotamers in the ratio 3:1), 4.11 and 3.99 (2s, 3H, rotamers in the ratio 1:3), 3.59 (s, 2H), 3.30 – 3.19 (m, 4H), 2.88 – 2.78 (m, 4H).

IR (Neat): 3318, 2942, 2833, 2113, 1757, 1519, 1453, 1385, 1324, 1245, 1205, 1142, 1010 cm^{-1}.

CI-MS (m/e): 391 (M^++2), 358, 331, 301

Example 133:

(1-{3-Fluoro-4-[4-(N-hydroxycarbamimidoylmethyl)-piperazin-1-yl]-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid-O-methyl ester



The title compound (35 mg, 32 %) was synthesized from compound (100 mg, 0.26 mmol), obtained in example 132, by following the procedure as described in example 86.

^{1}H NMR (200 MHz, DMSO): δ 9.75 – 9.65 (m, 1H), 9.01 (s, 1H), 8.65 and 8. 59 (2s, 1H, rotamers in the ratio 3:1), 7.84 – 7.60 (m, 2H), 7.22 (t, J = 8.9 Hz, 1H), 5.26 (s, 2H), 4.72

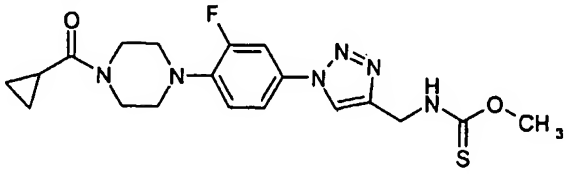
and 4.42 (2d, J = 5.6 Hz, 2H, rotamers in the ratio 3:1), 3.94 and 3.88 (2s, 3H, rotamers in the ratio 1:3), 3.18 – 3.10 (m, 4H), 2.91 (s, 2H), 2.60 – 2.40 (m, 4H).

IR (KBr): 3460, 3359, 2924, 1674, 1521, 1441, 1405, 1338, 1228, 1194, 1060, 924 cm^{-1}.

ES-MS (m/e): 445.3 (M^++23), 423.4 (M^++1)

Example 134:

{1-[4-(4-Cyclopropanecarbonyl-piperazin-1-yl)-3-fluoro-phenyl]-1H-[1,2,3]triazol-4-ylmethyl}-thiocarbamic acid O-methyl ester



The title compound (100 mg, 30 %) was synthesized from compound [4-(4-azido-2-fluoro-phenyl)-piperazin-1-yl]-cyclopropyl-methanone (235 mg, 0.73 mmol), obtained in preparation 71, by following the same procedure as described in example 1.

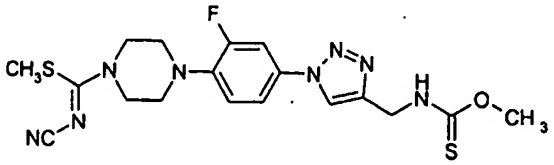
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 and 7.80 (2s, 1H, rotamers in the ratio 3:1), 7.50 (dd, J_1 = 2.6 Hz, J_2 = 12.6 Hz, 1H), 7.41 (dd, J_1 = 1.1 Hz, J_2 = 3.5 Hz, 1H), 7.03 (t, J = 8.8 Hz, 1H), 6.91 (bs, 1H), 4.91 and 4.65 (2d, J = 5.9 Hz, 2H, rotamers in the ratio 3:1), 4.11 and 4.00 (2s, 3H, rotamers in the ratio 1:3), 3.91 – 3.80 (m, 4H), 3.21 – 3.10 (m, 4H), 1.81 – 1.75 (m, 1H), 1.06 – 1.00 (m, 2H), 0.85 - 0.78 (m, 2H).

IR (KBr): 3444, 3224, 1614, 1521, 1443, 1327, 1233, 1144, 1039, 982, 871 cm^{-1}.

CI-MS (m/e): 419 (M^++1), 387,

Example 135:

4-{2-Fluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazine-1-carboximidothioic acid methyl ester, compound with acetonitrile



To a stirred solution of [1-(3-fluoro-4-piperazin-1-yl-phenyl)-1H-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid O-methyl ester (100 mg, 0.29 mmol), obtained in example 5, in ethanol was added dimethyl cyano dithioimino carbonate (46 mg, 0.31 mmol) and heated 9 to 13 hours at 60 °C . Ethanol was removed under vacuum and the residue was

diluted with ethylacetate and washed with water, brine and dried over Na_2SO_4. The organic layer was concentrated and the residue was purified by column chromatography (7:3 ethyl acetate/petroleum ether) to give the title product (32 mg, 25%).

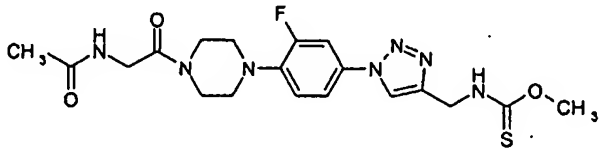
^{1}H NMR (200 MHz, DMSO + $CDCl_3$): δ 9.55 – 9.45 (m, 1H), 8.52 and 8.47 (2s, 1H, rotamers in the ratio 3:1), 7.80 – 7.60 (m, 2H), 7.16 (t, J = 8.8 Hz, 1H), 4.75 and 4.47 (2d, J = 5.8 Hz, 2H, rotamers in the ratio 3:1), 4.10 – 4.01 (m, 4H), 3.98 and 3.91 (2s, 3H, rotamers in the ratio 1:3), 3.39 – 3.19 (m, 4H), 2.76 (s, 3H).

IR (KBr): 3417, 2182, 1555, 1509, 1437, 1361, 1323, 1233, 1151, 876 cm^{-1}.

CI-MS (m/e): 449 (M^++1), 417

Example 136:

(1-{4-[4-(2-Acetylamino-acetyl)-piperazin-1-yl]-3-fluoro-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



The title compound (65 mg, 19 %) was synthesized from N-{2-[4-(4-azido-2-fluoro-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-acetamide (250 mg, 0.78 mmol), obtained in preparation 72, by following the procedure as described in example 1.

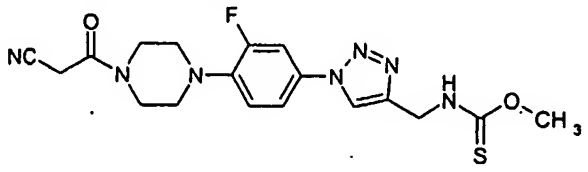
^{1}H NMR (200 MHz, DMSO + $CDCl_3$): δ 9.42 (bs, 1H), 8.45 and 8.39 (2s, 1H, rotamers in the ratio 3:1), 7.90 – 7.80 (m, 1H), 7.75 – 7.57 (m, 2H), 7.11 (t, J = 8.9 Hz, 1H), 4.77 and 4.49 (2d, J = 5.7 Hz, 2H, rotamers in the ratio 3:1), 4.06 (d, J = 5.0 Hz, 2H), 4.00 and 3.92 (2s, 3H, rotamers in the ratio 1:3), 3.78 – 3.60 (m, 4H), 3.35 – 3.05 (m, 4H), 1.96 (s, 3H).

IR (Neat): 3286, 1644, 1580, 1439, 1236, 1151, 1031, 868, 760 cm^{-1}.

CI-MS (m/e): 450 (M^++1), 418

Example 137:

(1-{4-[4-(2-Cyano-acetyl)-piperazin-1-yl]-3-fluoro-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



The title compound (70 mg, 51 %) was synthesized from 3-[4-(4-azido-2-fluoro-phenyl)-piperazin-1-yl]-3-oxo-propionitrile (95 mg, 0.33 mmol), obtained in preparation 73, by following the procedure as described in example 1

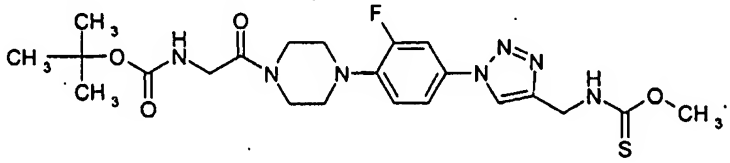
^{1}H NMR (200 MHz, DMSO + $CDCl_3$): δ 9.15 – 9.05 (m, 1H), 8.24 and 8.12 (2s, 1H, rotamers in the ratio 3:1), 7.60-7.45 (m, 2H), 7.07 (t, J = 8.5 Hz, 1H), 4.83 and 4.57 (2d, J = 5.6 Hz, 2H, rotamers in the ratio 3:1), 4.04 and 3.97 (2s, 3H, rotamers in the ratio 1:3), 3.82 – 3.70 (m, 4H), 3.65 – 3.60 (s, 2H), 3.25 – 3.03 (m, 4H).

IR (Neat): 3383, 1594, 1579, 1385, 1039 cm^{-1}.

CI-MS (m/e): 418 (M^++1), 386

Example 138:

[2-(4-{2-fluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazin-1-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester



The title compound (200 mg, 47 %) was synthesized from {2-[4-(4-azido-2-fluoro-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-carbamic acid tert-butyl ester (315 mg, 0.83 mmol), obtained in preparation 74, by following the procedure as described in example 1.

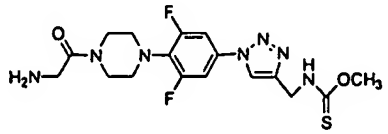
^{1}H NMR (200 MHz, $CDCl_3$): δ 8.04 and 7.80 (2s, 1H, rotamers in the ratio 3:1), 7.58 – 7.40 (m, 2H), 7.10 – 6.90 (m, 2H), 5.55 – 5.45 (m, 1H), 4.90 and 4.65 (2d, J = 5.8 Hz, 2H, rotamers in the ratio 3:1), 4.11 and 4.02 (2s, 3H, rotamers in the ratio 3:1), 3.91 (d, J = 7.0 Hz, 2H), 3.90 – 3.78 (m, 2H), 3.65 – 3.55 (m, 2H), 3.20 – 3.12 (m, 4H), 1.45 (s, 9H).

IR (Neat): 3379, 1647, 1419, 1157, 1028, 866 cm^{-1}.

CI-MS (m/e): 475 (M^+-32), 402, 376

Example 139:

(1-{4-[4-(2-Amino-acetyl)-piperazin-1-yl]-3-fluoro-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



The title compound (93 mg, 95 %) was synthesized from [2-(4-{2-fluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazin-1-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester (120 mg, 0.24 mmol), obtained in example 138, by treating with trifluoroacetic acid.

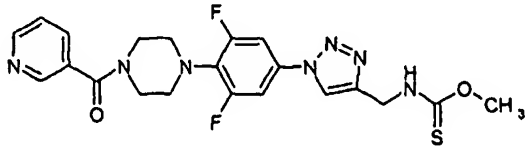
^{1}H NMR (200 MHz, DMSO): δ 9.70 (bs, 1H), 8.65 and 8.62 (2s, 1H, rotamers in the ratio 3:1), 8.30 – 8.01 (m, 2H), 7.90 – 7.68 (m, 2H), 7.22 (t, J = 8.9 Hz, 1H), 4.72 and 4.43 (2d, J = 5.4 Hz, 2H, rotamers in the ratio 3:1), 3.94 and 3.84 (2s, 3H, rotamers in the ratio 1:2), 3.75 – 3.65 (m, 2H), 3.60 – 3.50 (m, 2H), 3.19 – 3.01 (m, 6H).

IR (Neat): 3422, 1678, 1385, 1202, 1128, 1042, 833, 801, 721 cm^{-1}.

CI-MS (m/e): 408 (M^++1), 376

Example 140:

(1-{3,5-Difluoro-4-[4-(pyridine-3-carbonyl)-piperazin-1-yl]-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



The title compound (58 mg, 45%) was synthesized from [4-(4-azido-2,6-difluoro-phenyl)-piperazin-1-yl]-Pyridin-3-yl-methanone (130 mg, 0.38 mmol), obtained in preparation 75, by following the same procedure as described in example 1.

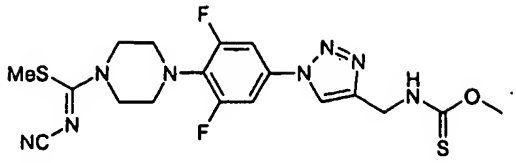
^{1}H NMR (200 MHz, DMSO): δ 9.75 – 9.61 (m, 1H), 8.75 – 8.60 (m, 3H), 7.89 (d, J = 7.8 Hz, 1H), 7.78 (d, J = 9.2 Hz, 2H), 7.50 (t, J = 5.3 Hz, 1H), 4.72 and 4.45 (2d, J = 5.6 Hz, 2H, rotamers in the ratio 3:1), 3.94 and 3.88 (2s, 3H, rotamers in the ratio 1:3), 3.81 – 3.60 (m, 2H), 3.55 – 3.39 (m, 2H), 3.39 – 3.10 (m, 4H).

IR (Neat): 3443, 2925, 1647, 1520, 1438, 1281, 1230, 1194, 1155, 1009, 852 cm^{-1}.

CI-MS (m/e): 442 (M^+-31), 314, 258

Example 141:

4-{2,6-Difluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazine-1-carboximidothioic acid methyl ester, compound with acetonitrile



The title compound (50 mg, 16 %) was synthesized from [1-(3, 5- difluoro-4-piperazin-1-yl-phenyl)-1H-[1, 2,3]triazol-4-ylmethyl]-thiocarbamic acid O-methyl ester (250 mg, 0.68 mmol), obtained in example 6, by following the procedure as described in example 135.

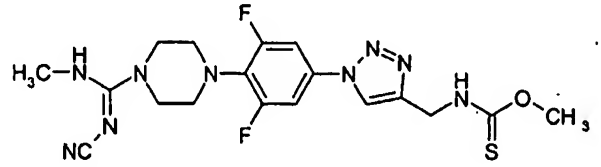
^{1}H NMR (200 MHz, $CDCl_3$): δ 8.06 and 7.89 (2s, 1H, rotamers in the ratio 3:1), 7.32 (d, J = 9.2 Hz, 2H), 6.95 – 6.85 (m, 1H), 4.90 and 4.57 (2d, J = 5.7 Hz, 2H, rotamers in the ratio 3:1), 4.11 and 3.99 (2s, 3H, rotamers in the ratio 1:3), 4.05 – 3.85 (m, 4H), 3.35 – 3.20 (m, 4H), 2.82 (s, 3H).

IR (KBr): 3392, 2181, 1551, 1224, 1028 cm^{-1}.

CI-MS (m/e): 467 (M^++1), 435

Example 142:

(1-{3,5-Difluoro-4-[4-(N-methylcarbamimidoyl)-piperazin-1-yl]-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester, compound with acetonitrile



To a stirred solution of 4-{2,6-difluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazine-1-carboximidothioic acid methyl ester (15 mg, 0.11 mmol), obtained in example 141, with acetonitrile was added dropwise methylamine in 40% water (0.02 mL) and stirred at 25-35 °C for 9 to 13 hours. The solvent was removed under vacuum and the residue was purified by column chromatography (7:3 ethyl acetate/petroleum ether) to give the title product (20 mg, 80%)

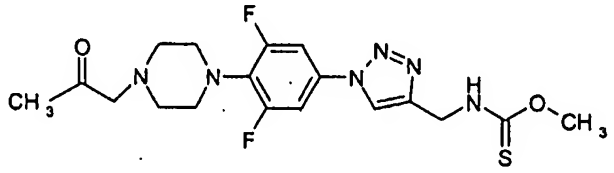
^{1}H NMR (200 MHz, $CDCl_3$): δ 8.07, 7.94 (2s, 1H, rotamers in the ratio 3:1), 7.29 (d, J = 10.1 Hz, 2H), 7.21 – 7.08 (m, 1H), 5.43 – 5.39 (m, 1H), 4.90 and 4.68 (2d, J = 5.7 Hz, 2H, rotamers in the ratio 3:1), 4.11 and 3.99 (2s, 3H, rotamers in the ratio 1:3), 3.68 – 3.52 (m, 4H), 3.42 – 3.21 (m, 4H), 3.08 (d, J = 4.8 Hz, 3H).

IR (Neat): 3281, 2925, 2967, 1578, 1430, 1286, 1229, 1120, 1030, 856, 756, 617, 558 cm^{-1}.

CI-MS (m/e): 450 (M^++1), 418

Example 143:

(1-{3,5-Difluoro-4-[4-(2-oxo-propyl)-piperazin-1-yl]-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



The title compound (65 mg, 45 %) was synthesized from 1-[4-(4-azido-2,6-difluoro-phenyl)-piperazin-1-yl]-propan-2-one (100 mg, 0.34 mmol), obtained in preparation 76, by following the procedure as described in example 1.

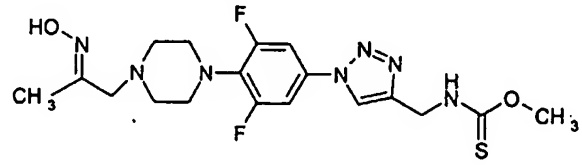
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 and 7.77 (2s, 1H, rotamers in the ratio 3:1), 7.27 (d, J = 10.4 Hz, 2H), 6.90 – 6.81 (m, 1H), 4.90 and 4.64 (2d, J = 6.0 Hz, 2H, rotamers in the ratio 3:1), 4.11 and 3.99 (2s, 3H, rotamers in the ratio 1:3), 3.37 – 3.32 (m, 4H), 3.26 (s, 2H), 2.65 – 2.53 (m, 4H), 2.19 (s, 3H).

IR (KBr): 3421, 2849, 1719, 1520, 1955, 1353, 1203, 1140, 1025, 843, 616 cm^{-1}.

CI-MS (m/e): 425 (M^++1), 393

Example 144:

(1-{3,5-Difluoro-4-[4-(2-hydroxyimino-propyl)-piperazin-1-yl]-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



The title compound (20 mg, 45 %) was synthesized from (1-{3,5-difluoro-4-[4-(2-oxo-propyl)-piperazin-1-yl]-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester (45 mg, 0.14 mmol), obtained in preparation 77, by following the procedure as described in example 1.

^{1}H NMR (400 MHz, DMSO + $CDCl_3$): δ 10.33 (bs, 1H), 9.31 – 9.30 (m, 1H), 8.45 and 8.40 (2s, 1H, rotamers in the ratio 3:1), 7.52 (d, J = 9.9 Hz, 2H), 4.78 and 4.51 (2d, J = 5.9

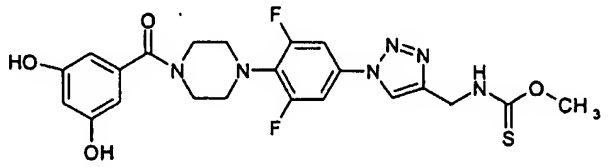
Hz, 2H, rotamers in the ratio 3:1), 4.01 and 3.94 (2s, 3H, rotamers in the ratio 1:3), 3.35 – 3.23 (m, 4H), 2.56 – 2.53 (m, 6H), 1.86 (s, 3H).

IR (KBr): 3444, 2925, 1635, 1457, 1040 cm^{-1}.

CI-MS (m/e): 440 (M^++1), 408

Example 145:

(1-{4-[4-(3,5-Dihydroxy-benzoyl)-piperazin-1-yl]-3,5-difluoro-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



The title compound (190 mg, 46 %) was synthesized from 3,5-dihydroxy benzoic acid (300 mg, 0.82 mmol) and [1-(3,5-difluoro-4-piperazin-1-yl-phenyl)-1H-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid O-methyl ester (300 mg, 0.82 mmol), obtained in example 6, by following the procedure as described in example 27.

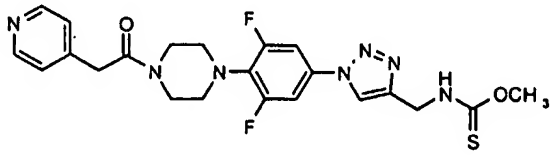
^{1}H NMR (400 MHz, DMSO): δ 9.66 – 9.61 (m, 1H), 8.71 and 8.67 (2s, 1H, rotamers in the ratio 3:1), 7.76 (d, J = 9.8 Hz, 2H), 6.27 (t, J = 2.0 Hz, 1H), 6.22 (d, J = 2.2 Hz, 2H), 4.72 and 4.44 (2d, J = 5.7 Hz, 2H, rotamers in the ratio 3:1), 3.95 and 3.88 (2s, 3H, rotamers in the ratio 1:3), 3.80 – 3.41 (m, 4H), 3.21 – 3.10 (m, 4H).

IR (KBr): 3263, 1583, 1518, 1442, 1337, 1280, 1230, 1154, 1033, 1007, 973, 858 cm^{-1}.

ES-MS (m/e): 527 (M^++23), 505 (M^++1).

Example 146:

(1-{3,5-Difluoro-4-[4-(2-pyridin-4-yl-acetyl)-piperazin-1-yl]-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



The title compound (200 mg, 81 %) was synthesized from 1-[4-(4-azido-2, 6-difluoro-phenyl) - piperazin-1-yl]-2-pyridin-4-yl-ethanone (320 mg, 0.89 mmol), obtained in preparation 78, by following the procedure as described in example 1.

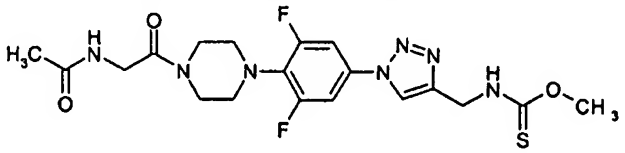
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (d, J = 5.9 Hz, 2H), 8.04 and 7.78 (2s, 1H, rotamers in the ratio 4:1), 7.29 (d, J = 9.1 Hz, 2H), 7.22 (d, J = 5.6 Hz, 2H), 6.91 – 6.85 (m, 1H), 4.90 and 4.64 (2d, J = 5.6 Hz, 2H, rotamers in the ratio 4:1), 4.11 and 3.99 (2s, 3H, rotamers in the ratio 1:5), 3.81 – 3.77 (m, 2H), 3.77 (s, 2H), 3.60 – 3.51 (m, 2H), 3.25 – 3.19 (m, 2H), 3.19 – 3.10 (m, 2H).

IR (KBr): 3443, 2923, 1630, 1519, 1455, 1203, 1038, 697 cm^{-1}.

CI-MS (m/e): 456 (M^+-31), 399

Example 147:

(1-{4-[4-(2-Acetylamino-acetyl)-piperazin-1-yl]-3,5-difluoro-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



The title compound (200 mg, 63 %) was synthesized from N-acetyl glycine (95 mg, 0.82 mmol) and [1-(3,5-difluoro-4-piperazin-1-yl-phenyl)-1H-[1,2,3] triazol-4-ylmethyl]-thiocarbamic acid O-methyl ester (250 mg, 0.68 mmol), obtained in example 6, by following the procedure as described in example 27.

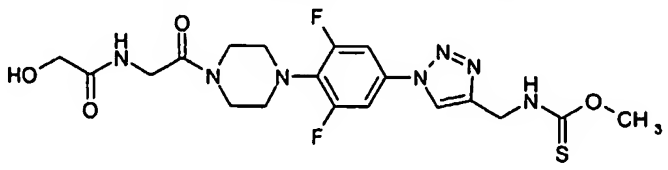
^{1}H NMR (400 MHz, DMSO): δ 9.65 (t, J = 5.6 Hz, 1H), 8.71 and 8.67 (2s, 1H, rotamers in the ratio 3:1), 7.96 (t, J = 5.3 Hz, 1H), 7.75 (d, J = 8.3 Hz, 2H), 4.72 and 4.43 (2d, J = 5.7 Hz, 2H, rotamers in the ratio 3:1), 3.98 (d, J = 5.6 Hz, 2H), 3.95 and 3.88 (2s, 3H, rotamers in the ratio 1:3), 3.60 – 3.51 (m, 4H), 3.20 – 3.10 (m, 4H), 1.87 (s, 3H).

IR (KBr): 3301, 2925, 1648, 1520, 1446, 1230, 1033, 983, 940, 857 cm^{-1}.

CI-MS (m/e): 468 (M^++1), 436, 394

Example 148:

[1-(3,5-Difluoro-4-{4-[2-(2-hydroxy-acetylamino)-acetyl]-piperazin-1-yl}-phenyl)-1H-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid O-methyl ester



The title compound (110 mg, 50%) was synthesized from N-{2-[4-(4-azido-2,6-difluoro-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-2-hydroxy-acetamide (160 mg, 0.46 mmol), obtained in preparation 81, by following the procedure as described in example 1.

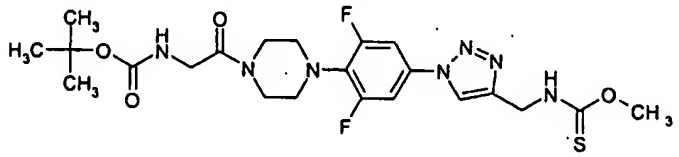
^{1}H NMR (400 MHz, DMSO): δ 9.65 (t, J = 5.8 Hz, 1H), 8.72 and 8.67 (2s, 1H, rotamers in the ratio 3:1), 7.75 (d, J = 8.3 Hz, 2H), 7.74 – 7.73 (m, 1H), 5.64 (t, J = 5.6 Hz, 1H), 4.73 and 4.44 (2d, J = 5.8 Hz, 2H, rotamers in the ratio 3:1), 4.06 (d, J =5.1 Hz, 2H), 3.95 and 3.89 (2s, 3H, rotamers in the ratio 1:3), 3.86 (d, J = 5.6 Hz, 2H), 3.61 – 3.50 (m, 4H), 3.21 – 3.10 (m, 4H).

IR (KBr): 3354, 2922, 1654, 1518, 1449, 1367, 1286, 1235, 1209, 1129, 1084, 1030, 983, 857, 759, 615, 580 cm^{-1}.

ES-MS (m/e): 506 (M^++23), 484 (M^++1).

Example 149:

[2-(4-{2,6-Difluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazin-1-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester



By following the procedure as described in example 82, the title compound (1.7 grams, 87%) was synthesized from {2-[4-(4-azido-2, 6-difluoro-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-carbamic acid tert-butyl ester (1.5 grams, 3.78 mmol), obtained in preparation 79.

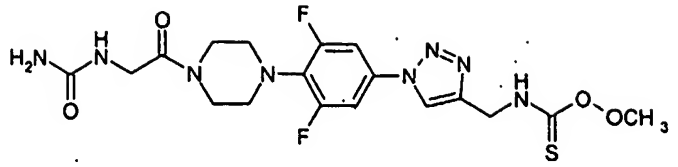
^{1}H NMR (400 MHz, DMSO): δ 8.06 and 7.82 (2s,1H, rotamers in the ratio 5:1), 7.31 (d, J= 9.2 Hz, 2H), 7.12 - 7.00 (m,1H), 5.62 -5.49 (m,1H), 4.91 and 4.66 (2d, J = 6.1 Hz, 2H, rotamers in the ratio 5:1), 4.14 – 3.99 (m, 5H), 3.82 -3.71 (m, 2H), 3.60 – 3.50 (m, 2H), 3.30 – 3.18 (m, 4H), 1.46 (s, 9H).

IR (KBr): 3287, 2976, 1716, 1844, 1517, 1464, 1367, 1280, 1228, 1022 cm^{-1}

ES-MS (m/e): 526(M^++1), 426

Example 150:

(1-{3,5-Difluoro-4-[4-(2-ureido-acetyl)-piperazin-1-yl]-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



[2-(4-{2,6-Difluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazin-1-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester (1.7 grams, 3.29 mmol), obtained in example 149, was treated with 60% TFA in DCM and stirred at 25-35 °C for 30 minutes and the reaction mixture was co-evaporated with toluene (2 x 30 mL) and extracted with ethyl acetate and concentrated to give (1-{4-[4-(2-amino-acetyl)-piperazin-1-yl]-3,5-difluoro-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester, which was pure enough to be taken for further step directly. To a stirred solution of (1-{4-[4-(2-amino-acetyl)-piperazin-1-yl]-3,5-difluoro-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O- methyl ester (270 mg, 0.73 mmol) in dry DCM at 0 °C was added trimethylsilyl isocyanate (0.3 mL, 2.2mmol) dropwise and stirred at 25-35 °C for 9 to 13 hours. The solvent was removed under vacuum and the residue was purified by column chromatography (1.5% Methanol in chloroform) to give the title product (150 mg, 44%).

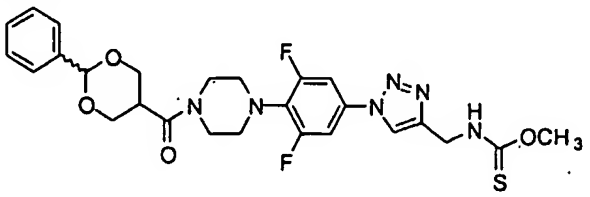
^{1}H NMR (400 MHz, DMSO): δ 9.65 (t, J = 5.6 Hz, 1H), 8.71 and 8.67 (2s, 1H, rotamers in the ratio 3:1), 7.75 (d, J = 9.9 Hz, 2H), 6.10 – 6.05 (m, 1H), 5.68 (s, 2H), 4.73 and 4.44 (2d, J = 5.9 Hz, 2H, rotamers in the ratio 3:1), 3.95 and 3.88 (2s, 3H, rotamers in the ratio 1:3), 3.92 (d, J = 5.1 Hz, 2H), 3.62 – 3.55 (m, 2H), 3.55- 3.50 (m, 2H), 3.20 – 3.10 (m, 4H).

IR (KBr): 3361, 2924, 1646, 1579, 1462, 1229, 1151, 1033, 817, 617 cm^{-1}.

ES-MS (m/e): 469 (M^++1)

Example 151:

(1-{3,5-Difluoro-4-[4-(2-phenyl-[1,3]dioxane-5-carbonyl)-piperazin-1-yl]-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester

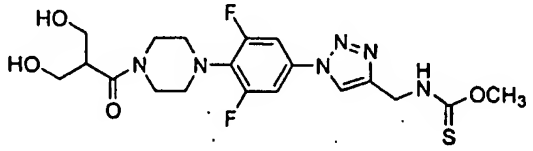


To a suspension of [1-(3,5-difluoro-4-piperazin-1-yl-phenyl)-1H-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid O-methyl ester (2.0 grams, 5.39 mmol) in DCM (30 mL) was added 2-phenyl-[1,3]dioxane-5-carboxylic acid (1.23 grams, 5.89 mmol) and *N*-methylmorpholine (0.78 mL, 7.1 mmol) followed by the addition of 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide.HCl (1.26 grams, 6.55 mmol) at 0 °C and stirred for 12 hours. The reaction mixture was diluted with DCM; washed with water and brine solution successively and then dried over Na_2SO_4. The DCM portion was concentrated and the resulting residue purified on silica gel (100-200 mesh) with $CHCl_3$/MeOH as eluent. The required compound was then dissolved in $CHCl_3$/MeOH. Charcoal was added and heated at 50 °C for 0.5 hour. Charcoal was filtered over celite and the filtrate concentrated and washed with petroleum ether. Title compound was obtained as light yellow solid (2.05 grams, 68%).

MS (m/z): 559 (M^++1), 527, 421.

Example 152:

(1-{3,5-Difluoro-4-[4-(3-hydroxymethyl-propionyl)-piperazin-1-yl]-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester



A cooled solution of aqueous HCl (50%, 50 mL) was added to a solution of (1-{3,5-difluoro-4-[4-(2-phenyl-[1,3]dioxane-5-carbonyl)-piperazin-1-yl]-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester (2.0 grams, 3.58 mmol), obtained in example 151, in methanol at 0 °C The temperature was allowed to come to 25-35 °C and stirring continued for 12 hours. Reaction mixture was neutralized with solid $NaHCO_3$ at 0 °C and then extracted with $CHCl_3$. The organic layer was washed with water and brine solution successively and dried over Na_2SO_4. The residue obtained upon concentration was purified over silica gel (100-200 mesh) with $CHCl_3$/MeOH as eluent. Title compound was obtained as white solid (960 mg, 57%).

Melting Point : 178-180 °C.

^{1}H NMR ($CDCl_3$+DMSO-d_6, 400 MHz): δ 8.76 & 8.63 (2t, J = 6.1 Hz, 1H), H), 8.21 & 8.07 (2s in a ratio of 4:1, 1H), 7.48 (d, *J* = 9.7 Hz, 2H), 4.85 & 4.56 (2d in a ratio of 4:1, *J*

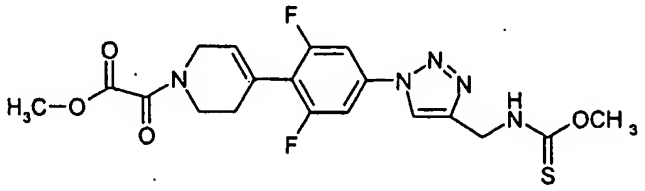
= 5.6 Hz, 2H), 4.05-4.21 (m, 1H), 4.03 & 3.96 (2s in a ratio of 1:4, 3H), 3.85 (d, J = 5.6 Hz, 4H), 3.75-3.72 (m, 4H), 3.25 (bs, 2H), 3.20 (bs, 2H).

IR (KBr, cm^{-1}): 3382, 3272, 1624, 1517, 1439, 1205, 1013, 981, 709.

MS (m/z): 471 (M^++1), 439, 391, 352.

Example 153:

(4-{2,6-Difluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazin –1-yl)-oxo-acetic acid methyl ester.



To a suspension of [1-(3,5-difluoro-4-piperazin-1-yl-phenyl)-1H-[1,2,3]triazol-4-ylmethyl]-thiocarbamic acid O-methyl ester (1.0 gram 2.72 mmol), obtained in example 6, in DCM was added triethyl amine (0.46 mL, 3.54 mmol) followed by the addition of methyl oxalyl chloride (0.31 mL, 3.37 mmol) at 0 °C and stirred for 0.5 hour. The reaction mixture was diluted with DCM; washed with water and brine solution successively and dried over Na_2SO_4. Organic portion was concentrated and purified on silica gel (100-200 mesh) with $CHCl_3$/MeOH as eluent. The title compound was obtained as white solid (865 mg, 70%).

Melting Point: 178-180 °C

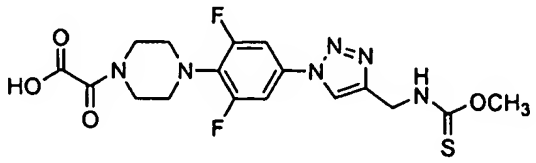
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.05 & 7.81 (2s in a ratio of 4:1, 1H), 7.31 (d, J = 9.3 Hz, 2H), 6.91 (bs, 1H), 4.93 & 4.65 (2d in a ratio of 4:1, J = 5.9 Hz, 2H), 4.11 & 4.00 (2s in aratio of 1:4, 3H), 3.90 (s, 3H), 3.72-3.82 (m, 2H), 3.55-3.65 (m, 2H), 3.15-3.35 (m, 4H).

IR (KBr, cm^{-1}): 3439, 3288, 1739, 1650, 1515.

MS (m/z): 469 (M^++1), 423.

Example 154:

(4-{2,6-Difluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazin –1-yl)-oxo-acetic acid



To a solution of (4-{2,6-difluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazin-1-yl)-oxo-acetic acid methyl ester (100 mg, 0.22 mmol), obtained in example 153, in THF was added lithium hydroxide (18 mg, 0.44 mmol) solution in water at 0 °C and stirred for 1 hour at 25-35 °C. Reaction mixture was diluted with water (2 mL) and pH of the solution was brought to 2 with 10% aqueous. HCl. Solid obtained was filtered and dissolved in aqueous.NaOH (13 mg, 0.33 mmol) solution. Aqueous layer was washed with ethyl acetate and acidified with 10% aquoes.HCl to pH 2. White solid obtained was filtered, washed with cold water and dried to obtain the title compound (60 mg, 62%).

Melting Point.: 160-162 °C .

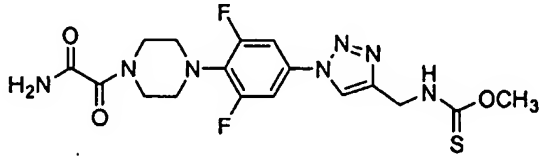
^{1}H NMR ($CDCl_3$+DMSO-d_6, 200 MHz): δ 8.85 (bs, 1NH), 8.25 & 8.13 (2s in a ratio of 4:1, 1H), 7.40 (d, J = 8.9 Hz, 2H), 4.85 & 4.59 (2d in a ratio of 4:1, J = 5.0 Hz, 2H), 4.06 & 4.00 (2s in a ratio of 1:4, 3H), 3.76 (bs, 2H), 3.66 (bs, 2H), 3.27 (bs, 4H).

IR (cm^{-1}): 3249, 1724, 1628, 1522, 1202, 1026, 856.

MS (m/z): 397, 365.

Example 155:

{1-[4-(4-Aminooxalyl-piperazin-1-yl)-3,4-difluoro-phenyl]-1*H*-[1,2,3]triazol-ylmethyl}-thiocarbamic acid *O*-methyl ester



To a solution of (4-{2,6-difluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazin-1-yl)-oxo-acetic acid (100 mg, 0.27 mmol), obtained in example 154, in THF was added triethyl amine (0.05 mL, 0.34 mmol) followed by the addition of isobutylchloroformate at 0 °C and stirred for 15 minutes. Ammonia gas was then passed through the reaction mixture for 15 minutes at 0 °C Reaction mixture was diluted with ethylacetate, washed with water and brine solution successively and dried over Na_2SO_4. Organic portion was concentrated and purified on silica gel (100-200 mesh) with $CHCl_3$/MeOH as eluent. The title compound was obtained as white solid (70 mg, 70%).

Melting Point: 190-192 °C.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.05 & 7.18 (2s in a ratio of 4:1, 1H), 7.31 (d, J = 9.0 Hz, 2H), 7.21 (bs, 1H), 7.07 (bs, 1H), 6.92 (bs, 1H), 4.91 & 4.66 (2d in a ratio of 4:1, J = 5.9 Hz, 2H), 4.20 - 4.30 (m, 2H), 4.11 & 4.00 (2s in a ratio of 1:4, 3H), 3.72-3.85 (m, 2H), 3.29 (bs, 4H).

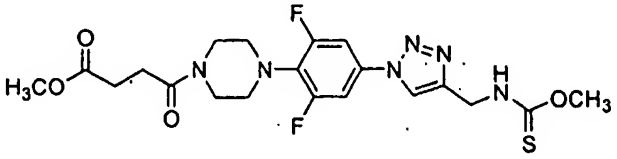
IR (KBr, cm^{-1}): 3381, 2924, 1659, 1517, 1232, 1028, 616.

MS (m/z): 440 (M^++1), 408.

The compounds mentioned below have been synthesized following any suitable procedure as defined above.

Example 156:

4-(4-{2,6-Difluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazin-1-yl)-4-oxo-butyric acid methyl ester



White colour solid (62% yield).

Melting Point.: 140-142 °C

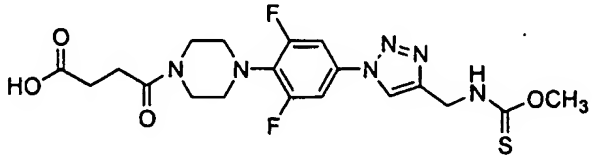
^{1}H NMR (DMSO-d_6, 200 MHz): δ 9.68 (bs, 1H), 8.73 & 8.68 (2s in a ratio of 1:4, 1H), 7.76 (d, J = 9.8 Hz, 2H), 4.73 & 4.43 (2d in a ratio of 4:1, J = 5.6 Hz, 2H), 3.95 & 3.89 (2s in a ratio of 1:4, 3H), 3.59 (s, 7H), 3.05-3.25 (m, 4H), 2.42-2.65 (m, 4H).

IR (KBr, cm^{-1}): 3245, 1720, 1641, 1518, 1454.

MS (m/z): 483 (M^++1), 451.

Example 157:

4-(4-{2,6-Difluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazin-1-yl)-4-oxo-butyric acid



White solid (62% yield).

Melting Point : 200-202 °C.

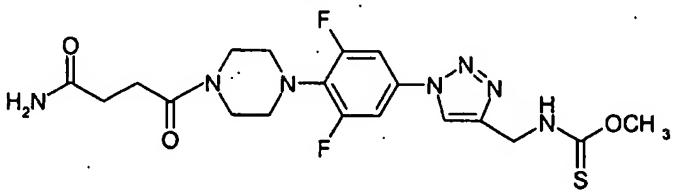
^{1}H NMR ($CDCl_3$+DMSO-d_6, 200 MHz): δ 11.8 (hump, 1H), 8.82 & 8.71 (2bs in a ratio of 1:4, 1H), 8.21 & 8.08 (2s in a ratio of 4:1, 1H), 7.88 (d, J = 9.3 Hz, 2H), 4.85 & 4.69 (2d in a ratio of 4:1, J = 5.9 Hz, 2H), 4.06 & 3.99 (2s in a ratio of 1:4, 3H), 3.74 (bs, 2H), 3.65 (bs, 2H), 3.22 (bs, 4H), 2.50-2.85 (m, 4H).

IR (KBr, cm^{-1}): 3311, 1713, 1601, 1521.

MS (m/z): 369, 337.

Example 158:

(1-{4-[4-(3-Carbamoyl-propionyl)-piperazin-1-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester



White solid (73% yield).

Melting Point: 180-182 °C .

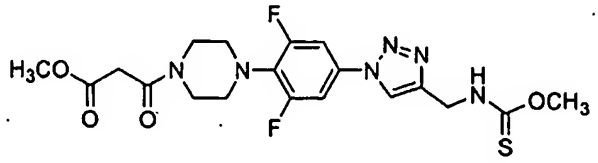
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.07 & 7.84 (2s in a ratio of 4:1, 1H), 7.31 (d, J = 9.5 Hz, 2H), 7.09 (bs, 1H), 6.05 (bs, 1H), 5.43 (bs, 1H), 4.90 & 4.66 (2d in a ratio of 4:1, J = 5.9 Hz, 2H), 4.11 & 4.00 (2s in a ratio of 1:4, 3H), 3.70-3.79 (m, 2H), 3.61-3.69 (m, 2H), 3.11-3.32 (m, 4H), 2.51-2.82 (m, 4H).

IR (KBr, cm^{-1}): 3393, 3220, 1636, 1519, 1432, 1204, 853, 613.

MS (m/z): 468 (M^++1), 436, 419

Example 159:

3-(4-{2,6-Difluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazin-1-yl)-4-oxo-propionic acid methyl ester



Melting Point.: 130-132 °C

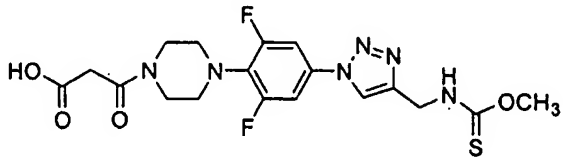
^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.07 & 7.83 (2s in a ratio of 4:1, 1H), 7.30 (d, J = 9.6 Hz, 2H), 7.02 (bs, 1H), 4.90 & 4.65 (2d in a ratio of 4:1, J = 5.9 Hz, 2H), 4.11 & 3.99 (2s in a ratio of 1:4, 3H), 3.78 (bs, 5H), 3.60 & 3.54 (m, 4H), 3.25 (bs, 4H).

IR (cm^{-1}): 3252, 1745, 1637, 1519, 1208, 1018, 856, 706.

MS (m/z): 469 (M^++1), 437.

Example 160:

3-(4-{2,6-Difluoro-4-[4-(methoxythiocarbonylamino-methyl)-[1,2,3]triazol-1-yl]-phenyl}-piperazin-1-yl)-4-oxo-propionic acid



Melting Point: 138-140 °C .

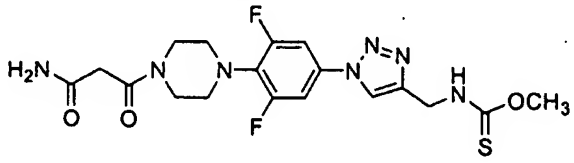
^{1}H NMR ($CDCl_3$+DMSO-d_6, 200 MHz): δ 12.5 (hump, 1H), 9.17 (bs, 1H), 8.36 & 8.28 (2s in a ratio of 4:1, 1H), 7.46 (d, J = 9.5 Hz, 2H), 4.82 & 4.54 (2d in a ratio of 4:1, J = 5.9 Hz, 2H), 4.04 & 3.96 (2s in a ratio of 1:4, 3H), 3.73-3.62 (m, 4H), 3.49 (s, 2H), 3.24 (bs, 4H).

IR (KBr, cm^{-1}): 3443, 3235, 1730, 1634, 1522, 1443, 1233, 859.

MS (m/z): 395, 379

Example 161:

(1-{4-[4-(2-Carbamoyl-acetyl)-piperazin-1-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester

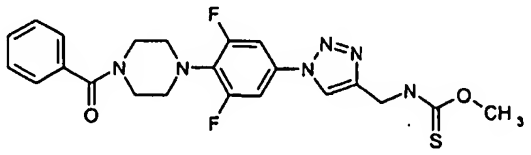


^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.65 (t, J = 5.9 Hz, 1H), 8.72 & 8.67 (2s in a ratio of 4:1, 1H), 7.76 (d, J = 9.5 Hz, 2H), 7.45 (bs, 1H), 6.99 (bs, 1H), 4.73 & 4.44 (2d in a ratio of 4:1, J = 5.6 Hz, 2H), 3.95 & 3.89 (2s in a ratio of 1:4, 3H), 3.58 (bs, 4H), 3.31 (s, 2H), 3.19 (bs, 2H), 3.11 (bs, 2H).

MS (ES): 476 (M^++22), 454 (M^+), 335, 276.

Example 162:

{1-[4-(4-Benzoyl-piperazin-1-yl)-3,5-difluoro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl}-thiocarbamic acid *O*-methyl ester:



Melting Point.: 132-140 °C .

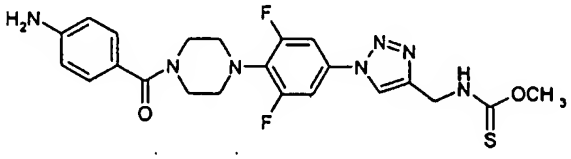
^{1}H NMR (200 MHz, $CDCl_3$): δ 8.06 & 7.80 (2s in a ratio of 4:1, 1H), 7.44 (s, 5H), 7.31 (d, J = 6.18 Hz, 2H), 7.01 (bs, 1H), 4.91 & 4.65 (2d in a ratio of 4:1, J = 5.9 Hz, 2H), 4.11 & 3.99 (2s in a ratio of 1:4, 3H), 3.81-3.98 (m, 2H), 3.51-3.70 (m, 2H), 3.11-3.38 (m, 4H).

IR (neat, cm^{-1}): 1625, 1518, 1437.

MS (m/e): 473 (M^+), 441.

Example 163:

(1-{4-[4-(4-Amino-benzoyl)-piperazin-1-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester:



Melting Point: 176-178 °C.

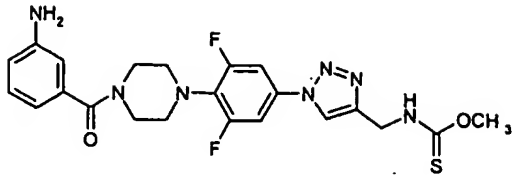
^{1}H NMR (200 MHz, $CDCl_3$): δ 8.05 & 7.80 (2s in a ratio of 4:1, 1H), 7.18-7.38 (m, 4H), 7.08 & 6.90 (2 bs in a ratio of 1:4, 1H), 6.68 (d, J = 8.4 Hz, 2H), 4.91 & 4.65 (2d in a ratio of 4:1, J = 5.9 Hz, 2H), 4.11 & 3.99 (2s in a ratio of 1:4, 3H), 3.65-3.85 (bs, 4H), 3.13-3.28 (bs, 4H).

IR (KBr, cm^{-1}): 3350, 1607, 1518, 1436.

MS (m/e): 488 (M^++1), 456, 424, 399.

Example 164:

(1-{4-[4-(3-Amino-benzoyl)-piperazin-1-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester:



Melting Point: 116-118 °C.

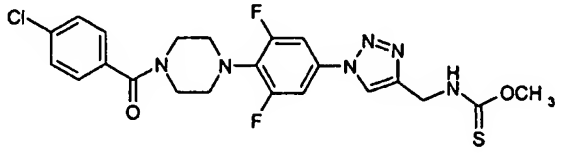
^{1}H NMR (200 MHz, $CDCl_3$): δ 8.05 & 7.80 (2s in a ratio of 4:1, 1H), 7.05-7.36 (m, 4H), 6.82-6.95 (m, 1H), 6.75 (t, J = 8.4 Hz, 2H), 4.89 & 4.65 (2d in a ratio of 4:1, J = 5.9 Hz, 2H), 4.11 & 3.99 (2s in a ratio of 1:4, 3H), 3.45-3.89 (m, 4H), 3.09-3.35 (m, 4H).

IR (KBr, cm^{-1}): 3357, 1623, 1518, 1463, 1437.

MS (m/e): 488 (M^++1), 456, 411.

Example 165:

(1-{4-[4-(4-Chloro-benzoyl)-piperazin-1-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester:



Melting Point: 180-184 °C .

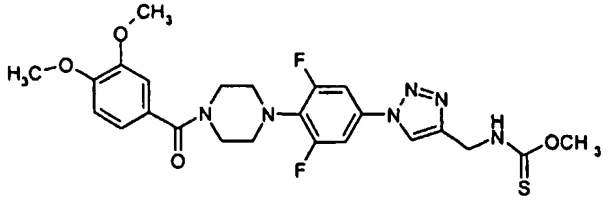
^{1}H NMR (200 MHz, $CDCl_3$): δ 8.05 & 7.80 (2s in a ratio of 4:1, 1H), 7.22-7.45 (m, 6H), 6.94 (bs, 1H), 4.91 & 4.65 (2d in a ratio of 4:1, J = 5.9 Hz, 2H), 4.11 & 3.99 (2s in a ratio of 1:4, 3H), 3.51-3.98 (m, 4H), 3.15-3.32 (m, 4H).

IR (KBr, cm^{-1}): 1638, 1519, 1433.

MS (m/e): 507 (M^+), 475, 391.

Example 166:

(1-{4-[4-(3,4-Dimethoxy-benzoyl)-piperazin-1-yl]-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid *O*-methyl ester:



Melting Point: 72-72 °C .

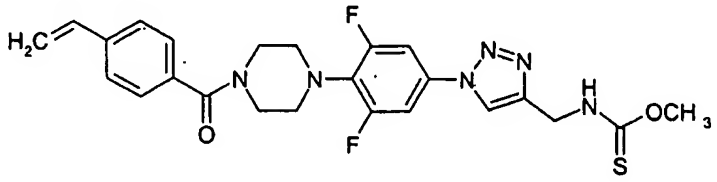
^{1}H NMR (200 MHz, $CDCl_3$): δ 8.06 & 7.81 (2s in a ratio of 4:1, 1H), 7.21-7.35 (m, 2H), 6.81-7.08 (m, 3H), 4.91 & 4.65 (2d in a ratio of 4:1, J = 5.9 Hz, 2H), 4.11 & 3.99 (2s in a ratio of 1:4, 3H), 3.92 (s, 6H), 3.65-3.85 (m, 4H), 3.18-3.32 (m, 4H).

IR (KBr, cm^{-1}): 2926, 1626, 1518, 1463.

MS (m/e): 533 (M^++1), 501.

Example 167:

(1-{3,5-Difluoro-4-[4-(4-vinyl-benzoyl)-piperazin-1-yl)-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl}-thiocarbamic acid *O*-methyl ester:



Melting Point: 150-152 °C .

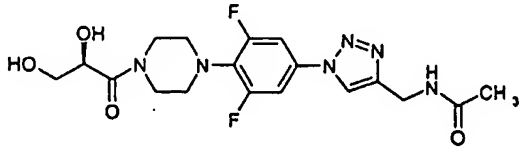
^{1}H NMR (200 MHz, $CDCl_3$): δ 8.05 & 7.80 (2s in a ratio of 4:1, 1H), 7.05-7.51 (m, 6H), 6.95 (bs, 1H), 6.65-6.82 (m, 1H), 5.73 (d, J = 17.4 Hz, 1H), 5.33 (d, J = 10.7 Hz, 1H), 4.91 & 4.65 (2d in a ratio of 4:1, J = 5.9 Hz, 2H), 4.11 & 3.99 (2s in a ratio of 1:4, 3H), 3.51-3.98 (m, 4H), 3.15-3.35 (m, 4H).

IR (KBr, cm^{-1}): 1636, 1560, 1519, 1432.

MS (m/e): 499 (M^+), 467, 380, 278.

Example 168:

***N*-(1-{4-[4-(2(*R*),3-Dihydroxy-propionyl)-piperazin-1-yl)-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl}-acetamide:**



Melting Point.: 182-184 °C.

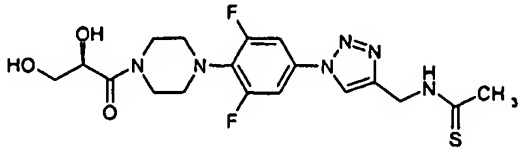
^{1}H NMR (200 MHz, DMSO-d_6): δ 8.66 (s, 1H), 8.44 (bs, 1H), 7.75 (d, J = 9.8 Hz, 2H), 5.02 (bs, 1H), 4.75 (bs, 1H), 4.35 (d, J = 5.3 Hz, 3H), 3.41-3.73 (m, 6H), 3.05-3.29 (bs, 4H), 1.86 (s, 3H).

IR (KBr, cm^{-1}): 1636, 1560, 1519, 1432.

MS (m/e): 425 (M^++1), 393, 337.

Example 169:

***N*-(1-{4-[4-(2(*R*),3-Dihydroxy-propionyl)-piperazin-1-yl)-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl}-thioacetamide:**



Melting Point: 202-203 °C.

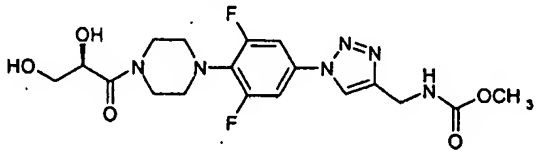
^{1}H NMR (200 MHz, DMSO-d_6): δ 10.50 (bs, 1H), 8.78 (s, 1H), 7.75 (d, J = 9.8 Hz, 2H), 5.00 (d, J = 7.0 Hz, 1H), 4.83 (d, J = 5.1 Hz, 2H), 4.74 (t, J = 5.8, 1H), 4.28-4.47 (m, 1H), 3.42-3.78 (m, 6H), 3.05-3.30, 2.44 (s, 3H).

IR (KBr, cm^{-1}): 1629, 1517, 1457.

MS (m/e): 441 (M^++1).

Example 170:

(1-{4-[4-(2(*R*),3-Dihydroxy-propionyl)-piperazin-1-yl)-3,5-difluoro-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl}-carbamic acid methyl ester:



Melting Point: 142-144 °C.

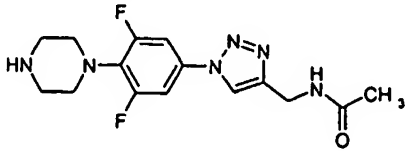
^{1}H NMR (200 MHz, DMSO-d_6): δ 8.67 (s, 1H), 7.77 (d, J = 9.6 Hz, 2H), 5.02 (bs, 1H), 4.75 (bs, 1H), 4.37 (bs, 1H), 4.31 (d, J = 5.6 Hz, 2H), 3.41-3.73 (m, 6H), 3.56 (s, 3H), 3.05-3.29 (bs, 4H).

IR (KBr, cm^{-1}): 1636, 1560, 1519, 1432.

MS (m/e): 441 (M^++1), 409.

Example 171:

***N*-[1-(3,5-Difluoro-4-piperazin-1-yl-phenyl)-1*H*-[1,2,3]triazol-4-ylmethyl}-acetamide:**



Melting Point.: 212 °C.

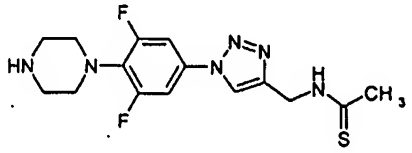
^{1}H NMR (200 MHz, DMSO-d_6): δ 8.68 (s, 1H), 8.51 (bs, 1H), 7.76 (d, J = 9.8 Hz, 2H), 4.35 (d, J = 5.6 Hz, 2H), 3.29 (bs, 4H), 3.04 (bs, 4H), 1.86 (s, 3H).

IR (KBr, cm^{-1}): 3278, 2928, 1676, 1520.

MS (m/e): 337 (M^++1).

Example 172:

***N*-[1-(3,5-Difluoro-4-piperazin-1-yl-phenyl)-1*H*-[1,2,3]triazol-4-ylmethyl}-thioacetamide:**



Melting Point: 210-212 °C

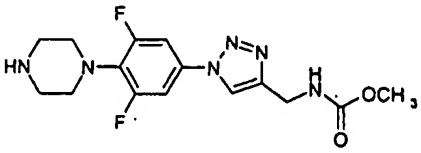
^{1}H NMR (200 MHz, DMSO-d_6): δ 10.56 (bs, 1H), 8.79 (s, 1H), 7.78 (d, J = 9.8 Hz, 2H), 4.84 (d, J = 5.1 Hz, 2H), 3.32 (bs, 4H), 3.10 (bs, 4H), 2.45 (s, 3H).

IR (KBr, cm^{-1}): 3437, 1518, 1559, 1037.

MS (m/e): 352 (M^+), 324, 279, 241.

Example 173:

[1-(3,5-Difluoro-4-piperazin-1-yl-phenyl)-1*H*-[1,2,3]triazol-4-ylmethyl}-carbamic acid methyl ester:



Melting Point : 110 °C.

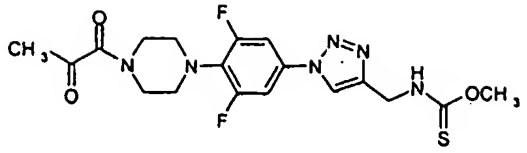
^{1}H NMR (200 MHz, DMSO-d_6): δ 8.65 (s, 1H), 7.72 (d, J = 9.8 Hz, 2H), 4.30 (d, J = 5.9 Hz, 2H), 3.56 (s, 3H), 3.17 (bs, 4H), 2.82 (bs, 4H).

IR (KBr, cm^{-1}): 1723, 1518, 1456, 1255.

MS (m/e): 353 (M^++1), 321.

Example 174:

(1-{3,5-Difluoro-4-[4-(2-oxo-propionyl)-piperazin-1-yl]-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl}-thiocarbamic acid *O*-methyl ester:



Melting Point: 126-128 °C.

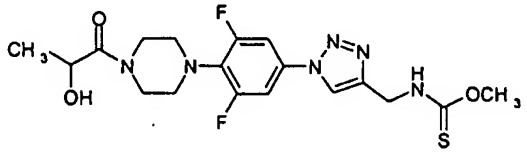
^{1}H NMR (200 MHz, $CDCl_3$): δ 8.06 & 7.81 (2s in a ratio of 4:1, 1H), 7.32 (d, J = 9.8 Hz, 2H), 6.93 (bs, 1H), 4.89 & 4.12 (2d in a ratio of 4:1, J = 6.18 Hz, 2H), 4.12 & 4.00 (2s in a ratio of 1:4, 3H), 3.72-3.85 (m, 2H), 3.58-3.3.70 (m, 2H), 3.18-3.32 (m, 4H), 2.48 (s, 3H).

IR (KBr, cm^{-1}): 1722, 1645, 1516.

MS (m/e): 406 (M^+-32), 395, 377, 335, 320.

Example 175:

(1-{3,5-Difluoro-4-[4-(2-hydroxy-propionyl)-piperazin-1-yl]-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl}-thiocarbamic acid *O*-methyl ester:



Melting Point: 130-132 °C

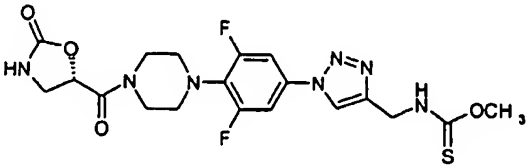
^{1}H NMR (200 MHz, $CDCl_3$): δ 8.06 & 7.34 (2s in a ratio of 4:1, 1H), 7.32 (d, J = 9.8 Hz, 2H), 6.96 (bs, 1H), 4.91 & 4.66 (2d in a ratio of 4:1, J = 5.9 Hz, 2H), 4.51 (q, J = 6.4 Hz, 1H), 4.11 & 3.99 (2s in a ratio of 1:4, 3H), 3.68-3.92 (m, 2H), 3.56 (bs, 2H), 3.25 (bs, 4H), 1.37 (d, J = 6.4 Hz, 3H).

IR (KBr, cm^{-1}): 3422, 1642, 1519.

MS (m/e): 440 (M^+), 408, 322

Example 176:

***S*-(1-{3,5-Difluoro-4-[4-(2-oxo-oxazolidine-5-carbonyl)-piperazin-1-yl]-phenyl}-1*H*-[1,2,3]triazol-4-ylmethyl}-thiocarbamic acid *O*-methyl ester:**



Melting Point : 158-160 °C

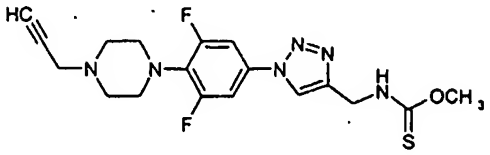
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 & 7.84 (2s in a ratio of 4:1, 1H), 7.25-7.39 (m, 2H), 6.98 (t, J = 7.25 Hz, 1H), 5.19-5.28 (m, 2H), 4.90 & 4.66 (2d in a ratio of 4:1, J = 6.2 Hz, 2H), 4.31-4.39 (m, 1H), 4.11 & 3.99 (2s in a ratio of 1:4, 3H), 3.82-4.00 (m, 2H), 3.62-3.75 (m, 2H), 3.21-3.32 (m, 4H).

IR (KBr, cm^{-1}): 1756, 1640, 1520.

MS (ES): 504 (M^++Na), 482 (M^++1).

Example 177:

{1-[3,5-Difluoro-4-(4-prop-2-ynyl-piperazine-1-yl)-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl}-thiocarbamic acid *O*-methyl ester



Melting Point: 120-121 °C

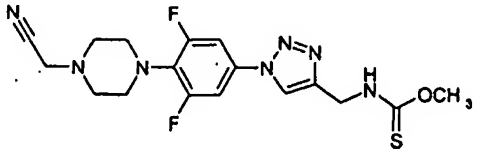
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 & 7.79 (2s in a ratio of 4:1, 1H), 7.22-7.31 (m, 2H), 6.93 (bs, 1H), 4.91 & 4.89 (2d in a ratio of 4:1, J = 5.9 Hz, 2H), 4.11 & 3.99 (2s in a ratio of 1:4, 3H), 3.38 (d, J = 2.4 Hz, 2H), 3.32 (bs, 4H), 2.68-2.78 (m, 4H), 2.29 (t, J = 2.4 Hz, 1H).

IR (KBr, cm^{-1}): 1518, 1455.

MS (m/e): 407 (M^++1), 375, 288.

Example 178:

{1-[4-(4-Cyanomethyl-piperazin-1-yl)-3,5-Difluoro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl}-thiocarbamic acid *O*-methyl ester



Melting Point: 130-131 °C .

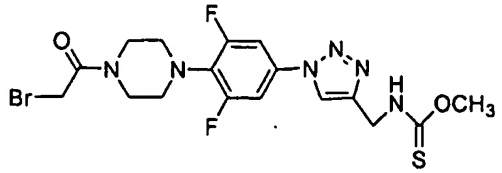
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 & 7.82 (2s in a ratio of 4:1, 1H), 7.29 (d, J = 9.8 Hz, 2H), 7.00 (bs, 1H), 4.90 & 4.66 (2d in a ratio of 4:1, J = 5.9 Hz, 2H), 3.58 (s, 2H), 3.26-3.33 (m, 4H), 2.71-2.81 (m, 4H).

IR (KBr, cm^{-1}): 2837, 1517, 1455.

MS (m/e): 408 (M^++1), 381, 376, 349.

Example 179:

(1-{4-[4-(2-Bromo-acetyl)-piperazin-1-yl]-3,5-difluoro-phenyl}-1H-[1,2,3]triazol-4-ylmethyl)-thiocarbamic acid O-methyl ester



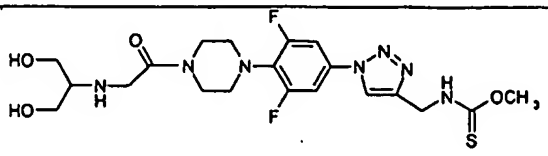
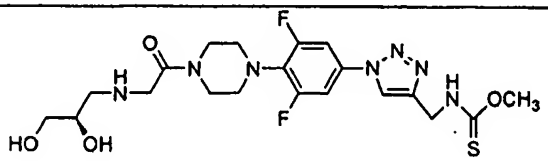
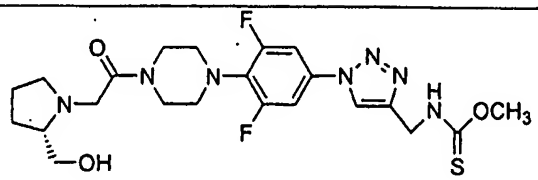
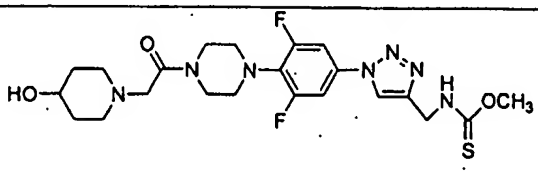
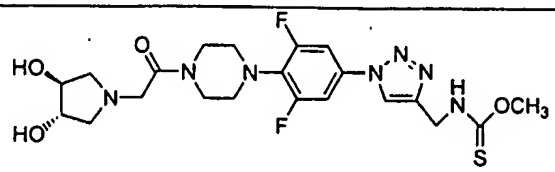
Bromoacetyl Bromide (2.354 grams, 11.7 mmol) was added drop wise (30 minutes) to a suspension of compound (2.8 grams, 11.7 mmol) obtained in example 6, and K_2CO_3 (0.967 grams, 7 mmol) in DCM (50 mL) at 0-5 °C. The reaction mixture was then stirred for 2 hours at 25-35 °C, concentrated and extracted the product in ethyl acetate (500 mL). The organic layer was washed with water (100 mL), brine (100 mL) and dried over Na_2SO_4 and concentrated to get brownish semisolid mass. Product was purified by column chromatography (60-120 mesh silica, 15 % ethyl acetate in hexanes, to get the product (1.1 grams, 26%) as a pale yellow solid.

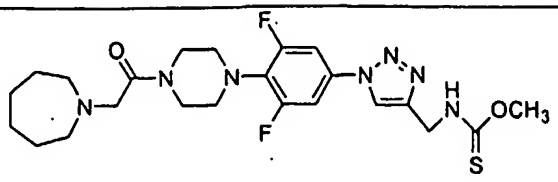
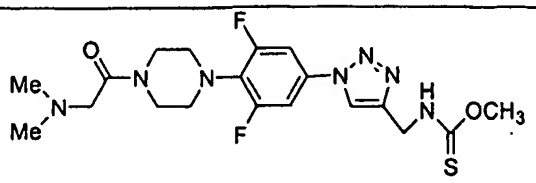
Example 180-186

For secondary Amine: Secondary amine (1-1.5 equivalents) was added to a suspension of starting compound (1 equivalent) and K_2CO_3 (2-3 equivalnets) in Acetonitrile (CH_3CN) (40-50 v/w) at 25-30 °C . The reaction mixture was stirred for (1-8 hours). Reaction was monitored by TLC and after the completion, product was extracted with ethyl acetate and usual workup gave nearly pure product which was taken to the next step without further purification.

For primary Amine: A solution of the starting material (1 equivalant) in CH_3CN (20-30 v/w) was added drop wise to a suspension of primary amine (5-10 equivalents) & K_2CO_3 (3-5 equivalents) in CH_3CN (30-50 v/w) at 0-5 °C . Reaction mixture was then stirred for (1-8 hours) at 25-35 °C and monitored by TLC. Product was extracted with ethyl acetate and usual workup gave crude product, which was further purified by column chromatography.

The following compounds were prepared by following the above procedure.

Ex. No.	Compound	Analytical data
180		^{1}H NMR (400 MHz, DMSO-d_6): δ 9.65-9.63 (m, 1H), 8.72 & 8.67 (2s, 1H, rotamers), 7.78 (d, J = 9.9 Hz, 2H), 4.74 & 4.44 (2d, J = 5.6 Hz, 2H, rotamers), 4.51-4.49 (m, 2H), 3.95 & 3.88 (2s, 3H, rotamers), 3.85-3.05 (m, 15H), 2.61-2.55 (m 1H).
181		^{1}H NMR (400 MHz, DMSO-d_6) : δ 9.65-9.63 (m, 1H), 8.72 & 8.67 (2s, 1H, rotamers), 7.78 (d, J = 9.9 Hz, 2H), 4.74 & 4.44 (2d, J = 5.6 Hz, 2H, rotamers), 4.61-4.51 (m, 2H), 3.95 & 3.88 (2s, 3H, rotamers), 3.65-3.00 (m, 11H), 2.71-2.41 (m, 4H).
182		^{1}H NMR (400 MHz, DMSO-d_6) : δ 9.65-9.63 (m, 1H), 8.72 & 8.67 (2s, 1H, rotamers), 7.78 (d, J = 9.9 Hz, 2H), 4.74 & 4.44 (2d, J = 5.6 Hz, 2H, rotamers), 4.91 (bs, 1H), 3.95 & 3.88 (2s, 3H, rotamers), 3.61-3.00 (m, 14H), 2.61- 2.52 (m, 4H).
183		^{1}H NMR (400 MHz, DMSO-d_6): δ 9.65-9.63 (m, 1H), 9.45 (bs, 1H), 8.72 & 8.67 (2s, 1H, rotamers), 7.78 (d, J = 9.9 Hz, 2H), 4.74 & 4.44 (2d, J = 5.6 Hz, 2H, rotamers), 4.41-4.20 (m, 2H), 3.95 & 3.88 (2s, 3H, rotamers), 3.81-2.90 (m, 14H), 1.91-1.80 (m, 2H), 1.80-1.61 (m, 2H).
184		^{1}H NMR (400 MHz, DMSO-d_6): δ 9.65-9.63 (m, 1H), 8.72 & 8.67 (2s, 1H, rotamers), 7.78 (d, J = 9.9 Hz, 2H), 4.74 & 4.44 (2d, J = 5.6 Hz, 2H, rotamers), 4.66 (m, 2H), 3.95 & 3.88 (2s, 3H, rotamers), 3.93-3.91 (m, 2H), 3.8-2.8 (m, 12H), 2.25-2,23 (m, 2H).

185		^{1}H NMR (400 MHz, DMSO-d_6): δ 9.65-9.63 (m, 1H), 8.72 & 8.67 (2s, 1H, rotamers), 7.78 (d, J = 9.9 Hz, 2H), 4.74 & 4.44 (2d, J = 5.6 Hz, 2H, rotamers), 3.95 & 3.88 (2s, 3H, rotamers), 3.60-3.40 (4H, m), 3.22 (s, 2H), 3.31-3.00(4H, m) 1.51-1.41 (m, 8H).
186		^{1}H NMR (400 MHz, DMSO-d_6) : δ 9.65-9.63 (m, 1H), 8.72 & 8.67 (2s, 1H, rotamers), 7.78 (d, J = 9.9 Hz, 2H), 4.74 & 4.44 (2d, J = 5.6 Hz, 2H, rotamer), 3.95 & 3.88 (2s, 3H, rotamer), 3.71-3.52 (m, 4H), 3.31-3.00 (m, 6H), 2.21 (s, 6H).

Example 187

Minimum Inhibiton Concentrations (MICs) were determined by broth microdilution technique as per the guidelines prescribed in the fifth edition of Approved Standards, NCCLS document *M7-A5 Vol 20 - No 2, 2000* Villinova, PA.

Initial stock solution of the test compound was prepared in DMSO. Subsequent two fold dilutions were carried out in sterile Mueller Hinton Broth (Difco) (MHB).

Frozen cultures stocks were inoculated into 50 ml sterile MHB in 250 ml Erlyn Meyer flasks.

Composition of MHB is as follows:

Beef Extract Powder - 2.0 g/litre

Acid Digest of Casein - 17.5 g/ litre

Soluble Starch - 1.5 g/litre

Final pH 7.3 ± 0.1

Flasks were incubated for 4 to 5 h at 35 °C on a rotary shaker at 150 rpm. Inoculum was prepared by diluting the culture in sterile MHB to obtain a turbidity of 0.5 McFarland standard. This corresponds to 1-2 x 10^8 CFU/ml. The stock was further diluted in sterile broth to obtain 1-2 X 10^6 CFU/ml. 50 µl of the above diluted inoculum was added from 1-10 wells. The plates were incubated 9 to 13 hours at 37 °C.

MIC is read as the lowest concentration of the compound that completely inhibits growth of the organism in the microdilution wells as detected by the unaided eye.

Organism	Culture No.	DRCC No.

Staphylococcus aureus	ATCC 33591	019
Staphylococcus aureus	ATCC 49951	213
Staphylococcus aureus	ATCC 29213	035
Enterococcus faecalis	ATCC 29212	034
Enterococcus faecalis	NCTC 12201	153
Enterococcus faecium	NCTC 12202	154
Escherichia coli	ATCC 25922	018
Haemophilus influenzae	ATCC 49247	432
Haemophilus influenzae	ATCC 49766	433
Haemophilus influenzae	ATCC 9006	529
Moraxella catarrhalis	ATCC 25238	300
Streptococcus pneumoniae	ATCC 6303	236
Streptococcus pneumoniae	ATCC 49619	237
Streptococcus pneumoniae	ATCC 700673	238
S.aureus - MRSA	-	446
S.aureus - MRSA	-	448
S.aureus - MRSA	-	449
Corynebacterium jeikeium		
Viridans Streptococci		

ATCC: American Type Culture Collection, USA

NCTC: National Collections of Type Cultures, Colindale, UK

DRCC: Dr. Reddy's Culture Collection, Hyderabad, India.

The *in vitro* antibacterial activity data is shown in TABLE 1.

Example 188:

- *S.aureus* ATCC 29213 and other tested strains were grown 9 to 13 hours on Columbia Blood agar (DIFCO).
- The inoculum was prepared by suspending the culture in 0.9% saline and adjusted to 100 x LD_{50} dose in 10% Hog Gastric Mucin (DIFCO). 0.5ml was injected intraperitonially to Swiss albino mice weighing 18-22g (n=6)
- Test compounds were solubilised in suitable formulation and 0.25ml was administered intra venously or orally or sub-cutaneously at 1 hr and 5 hr post infection by BID or TID or single dose protocol
- The animals were observed for 5-7 days and the survival was noted.
- ED_{50} was calculated by probit analysis.

Abbreviations:

$CHCl_3$: Chloroform

Na_2CO_3: Sodium carbonate

$NaHCO_3$:	Sodiumbicarbonate
HCl:	Hydrochloride
TFA:	Trifluoro acetic acid
TBDMSO:	*tert*-butyl-dimethyl-silanyloxy)-acetyl chloride
DCM:	Dichloromethane
EDCI:	1-[3-(dimethylamino)propyl]-3-ethyl- carbodiimide, hydrochloride
DMF:	Dimethylformamide
THF:	Tetrahydrofuran
$(BOC)_2O$:	Di-*tert*-butyl Dicarbonate
mL:	Milli litres
mmol:	Milli moles
Et_3SiH:	Triethylsilane
$BF_3.OEt_2$:	Boron trifluoride diethyl ether complex
CH_3COOH:	Trifluoroacetic acid
TMSCl:	Trimethylsilyl chloride
NaI:	Sodiumiodide
Me_2SiI_2:	Diiododimethyl silane
Bu_3SnH:	Tri-n-butyl tin hydride
CuI:	Cuprous (1) Iodide